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OBSERVATIONS ON PHENYLKETONURIA IN ONTARIO

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IT IS now generally agreed that, although the most prominent feature of phenylketonuria is mental deficiency, the primary lesion is an inborn error of metabolism. Patients with phenylketonuria are unable to metabolize phenylalanine adequately because of a deficiency of the enzyme phenylalanine hydroxylase. In consequence, phenylalanine accumulates in the blood and various phenylalanine metabolites appear in the urine. One of these metabolites is phenylpyruvic acid which gives a characteristic green colour with ferric chloride and so provides a simple means of identifying the disease.

In the last few years it has become clear that the early treatment of phenylketonuria with a low phenylalanine diet will prevent the development of mental defect.[1] For this reason alone phenylketonuria has assumed an importance out of proportion to its actual frequency.

Several full reviews of phenylketonuria have been published[2-5] but relatively few observations about the disease have been reported from Canada. This paper describes some studies on a series of 98 phenylketonuric patients, all of whom came from Ontario.

MATERIAL AND METHODS

The series was made up of 98 patients with phenylketonuria drawn from three main sources. The first group (20 cases) were patients seen at the Hospital for Sick Children, Toronto. The second group (50 cases) were inpatients at the Ontario Hospital Schools at Orillia, Ontario (33 cases), and Smiths Falls, Ontario (17 cases). The third group (28 cases) consisted of 17 patients known only by hospital case-notes and 11 patients known by case-notes and interviews or correspondence with the parents. All of the patients were, or had been, resident in Ontario. Limited observations on 44 of these patients have been published previously.[6-9]

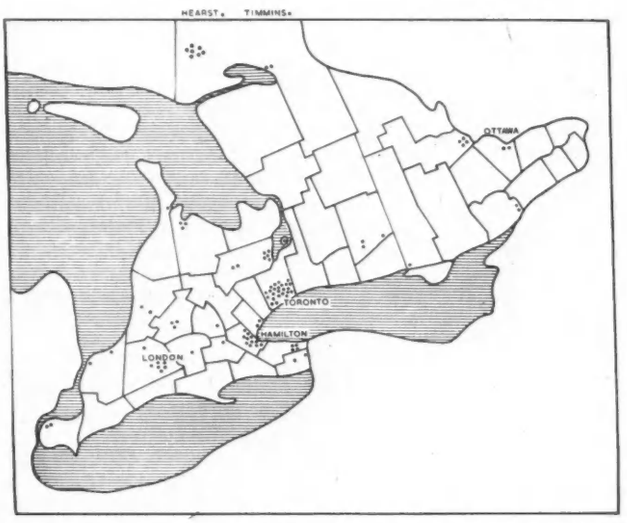

Fig. 1.—Phenylketonuria in Ontario. Present geographical location or that just prior to hospitalization. Each dot represents one patient.

In all cases, except one, the diagnosis was made by testing the urine for phenylpyruvic acid with ferric chloride or Phenistix. In the one exception (Case 2, Table II), there was strong circumstantial evidence for the diagnosis (a phenylketonuric sibling, mental retardation, fair hair, blue eyes, infantile eczema). A significantly raised fasting plasma phenylalanine level was demonstrated in 69 patients (method of Udenfriend and Cooper[10]).

INCIDENCE AND LOCATION

Several estimates have been made of the incidence of phenylketonuria in populations of predominantly European descent.[2, 11, 12] These agree reasonably well and vary from 2 to 6 per 100,000 persons, with an average of 4 per 100,000 or 1 in 25,000. On this basis, Ontario, with a population in 1960 of just over six million, should have some 240 cases. It seems clear that the 83 living patients from this series represent only about one-third of the phenylketonuric subjects in the province.

Although the incidence of phenylketonuria in the general population is about 0.004%, most patients with phenylketonuria eventually find their way to institutions for retarded children and here form from 0.1 to 2.7% of the population.[2] In

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TABLE I.—ESTIMATED NUMBER OF CHILDREN WITH PHENYLKETONURIA BORN 1959 - 1974, ONTARIO

Year	*Estimated* live births (thousands)*	*Number‡ born with phenyl-ketonuria*	*Number still§ alive this year with phenyl-ketonuria*	*Number born and alive this year with phenyl-ketonuria*
1959	157†	6	—	6
1960	162	6	6	12
1961	166	7	12	19
1962	171	7	19	26
1963	176	7	26	33
1964	181	7	32	39
1965	185	7	39	46
1966	190	8	46	54
1967	195	8	54	62
1968	199	8	62	70
1969	204	8	69	77
1970	209	8	77	85
1971	214	9	85	94
1972	218	9	93	102
1973	223	9	102	111
1974	228	9	110	119
		123		

*Assuming an average annual increase of 4700 live births.
†Tentative figure, Registrar-General's office.
‡Based on 4 per 100,000 born with this condition.
§Based on Ontario Life Table, Dominion Bureau of Statistics, 1956.

this series, 50 phenylketonuric individuals were found in two Ontario Hospital Schools with a combined population (in 1959) of 5061, an incidence of 1%.

Fig. 1 shows the geographical distribution of the cases in this series. The positions indicated refer to the present location of the patient or that just prior to hospitalization. In general, most of the patients came from the most densely populated areas. The small clusters of cases in outlying areas usually reflect the fact that more than one case may be found in the same family.

Using a birth rate of 1 phenylketonuric per 25,000 births and best current estimates of population increase and mortality, Dr. A. H. Sellers of the Division of Medical Statistics, Ontario Department of Health, has made an estimate of the number of children with phenylketonuria who have been, or will be, born in Ontario between 1959 and 1974 (Table I). It can be seen that in these 15 years some 123 new cases of phenylketonuria are to be expected.

TABLE II.—PHENYLKETONURIA: AGE DISTRIBUTION OF THE 83 LIVING PATIENTS

Age group	*Number of patients*			
	Male	*Female*	*Total*	*%*
0 - 4	10	10	20	24
5 - 9	10	13	23	28
10 - 14	10	6	16	19
15 - 19	1	5	6	7
20 - 24	1	3	4	5
25 - 29	0	3	3	4
30 - 34	4	0	4	5
35 - 39	0	4	4	5
40 - 44	0	2	2	2
45 - 49	0	0	0	0
50 - 54	1	0	1	1
Totals	37	46	83	100

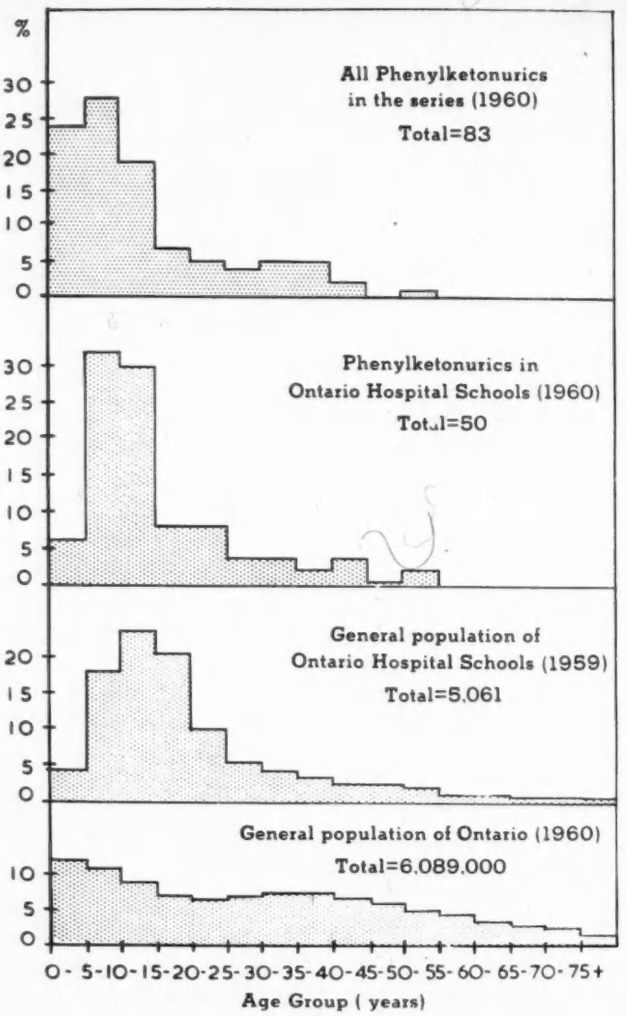

Fig. 2.—Phenylketonuria. Comparison of percentage age distributions of the whole series, the phenylketonuric patients in the Ontario Hospital Schools, the general population of these schools and the general population of Ontario.

MORTALITY

The foregoing estimate is based on an average life expectancy. There is some evidence from the age distribution of reported cases of phenylketonuria that the life expectancy of untreated patients is diminished.[5] Table II shows the age and sex distribution of the 83 living patients in this series. The percentage age distribution is compared with the percentage age distribution of the general population of Ontario in the top and bottom sections of Fig. 2. It can be seen that, compared with the general population, there is a relative excess of the younger phenylketonurics and a relative deficiency of the older patients. This is presumably due to an increased mortality in phenylketonuria, but other factors may be involved.[13]

This type of age distribution is characteristic of mental defect in general.[13] Since the great majority of untreated phenylketonurics are mentally defective, a further comparison can be made between the age distribution of the phenylketonurics in the Ontario Hospital Schools and the age distribution of the general population of these schools. This is shown in the middle two sections of Fig. 2. There

TABLE III.—PHENYLKETONURIA: AGE AND CAUSE OF DEATH IN 15 PATIENTS

Patient	*Sex*	*Age in years*	*Autopsy*	*Cause of death*	*Clinical history*
1. W.W.	M	8/12	Yes	Pneumonia	Severe infantile eczema
2. S.F.	F	1 5/12	No	Unknown	Found dead in bed. Infantile eczema
3. J.S.	M	3 5/12	Yes	Acute interstitial pneumonia	Sudden death. Severe infantile eczema
4. D.Wa.	F	3 7/12	Yes	Staphylococcal septicemia with skin lesions, empyema, renal abscesses	Pre-terminal measles and bronchopneumonia
5. D.F.	F	4 5/12	No	Pneumonia	Infantile eczema. Sib of S.F.
6. D.So.	F	4 10/12	Yes	Lobar pneumonia	Mild infantile eczema
7. V.I.	M	8	Yes	Lobar pneumonia	
8. J.V.	M	11	Yes	Bronchopneumonia	5 previous attacks of pneumonia
9. W.H.	M	12	Yes	Uremia, chronic pyelonephritis, terminal bronchopneumonia	
10. C.T.	M	16	Yes	Bronchopneumonia	2 attacks of bronchitis
11. M.L.	F	17	No	"Exhaustion and intestinal intoxication"	
12. M.Ta.	F	19	No	Diabetic coma	
13. G.T.	M	22	Yes	Bronchopneumonia and empyema	Sib of C.T.
14. I.H.	F	26	No	Repeated convulsions associated with measles	
15. R.Ta.	M	28	Yes	Ruptured esophageal ulcer and hemothorax. Duodenal ulcer found	Sib of M.Ta.

is obviously less discrepancy between the two age distributions, and a comparison of the absolute figures by a chi-square test showed that there was no significant difference.

Observations on the age and causes of death in phenylketonuria are scanty.[5] Table III gives some of these details for 15 patients. Most of the data were taken from case records of the Ontario Hospital Schools.

In 8 of the 15 cases the cause of death was ascribed to an acute respiratory disease, and pneumonia was cited as a contributory cause in two others. Two patients had a past history of repeated respiratory infections. Two deaths were associated with measles. Two deaths were sudden and were largely unexplained. It is of great interest that five of the six children under the age of five years had a definite history of infantile eczema.

Cases 12 and 15 were patients from an interesting family originally described by Penrose.[7] There were 12 children in the sibship of whom five were shown by Penrose to have phenylketonuria. This was also a likely diagnosis in a sixth sib who had died as a young child. Three of the affected sibs are still alive. Case 15 died suddenly in 1959 from a ruptured esophageal ulcer and a massive hemothorax; an associated duodenal ulcer was found. Case 12, the youngest sib, had diabetes mellitus as well as phenylketonuria. The diabetes began at the age of four years and she was admitted to the Hospital for Sick Children, Toronto, on five occasions, once in coma, for regulation and readjustment of her diet and insulin. She died in coma in 1952, 48 hours after discontinuing insulin on the advice of a religious fanatic.

ASSOCIATED CONDITIONS

Single cases of phenylketonuria have been reported in association with neurofibromatosis,[14] Gower's muscular dystrophy,[15] diabetes mellitus,[7] and polydactyly.[9] Jervis[16] found three cases of congenital dislocation of the hip in a survey of 200 phenylketonuric subjects. Six phenylketonuric babies are now reported to have had a Ramstedt operation for pyloric stenosis.[9, 17] It seems likely that the association of phenylketonuria with these conditions is no more than coincidental. There is a closer relationship between phenylketonuria and infantile eczema.

Infantile Eczema

Folling,[18] in his original description of phenylketonuria, found that four of 10 patients had rough, dry skins with papular or eczematous lesions. Other workers have noted a tendency to dermatitis,[2, 7] dermatographia or urticaria factitia,[3, 19] photosensitivity[19] or eczema, and eczema is now regarded as an integral part of the clinical picture of phenylketonuria. According to Knox,[5] the incidence of eczema in published series of phenylketonurics varies from 17% to 34%. It is not always clear from the reported cases what skin diseases the patients did suffer from or whether these were any different from the skin lesions often found in badly retarded patients with poor hygiene.[3] In this series, particular attention was paid to the occurrence of infantile eczema.

By infantile eczema in this context is meant a skin lesion starting in the first 18 months of life and characterized by itching, erythema, papules and vesicles, oozing, crusting and lichenification. Secondary infection is common. The course of the disease is protracted and marked by remissions and exacerbations. In general, the lesions in the younger child tend to be mainly exudative and are found on the face and trunk, whereas in the older child the lesions tend to be drier and are often confined to the flexures.

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The series was divided into two groups according to whether the dermatological history was regarded as adequate or inadequate. The term adequate implied that the history had been taken personally or that the hospital case records were explicit about the presence or absence of infantile eczema. Forty-three patients were thought to have adequate dermatological histories and of these 13 (31%) had a history of infantile eczema (Table IV). This is probably an overestimate of the overall incidence, since those children who had eczema would be more likely to have hospital records describing the state of the skin. Fifty-five patients were thought to have inadequate dermatological histories and of these 3 (6%) were said to have had infantile eczema. This is probably an underestimate because the hospital records were mainly concerned with the neurological and social aspects of the patients' histories. The combined incidence of infantile eczema in the two groups was 16%.

TABLE IV.—PHENYLKETONURIA. THE MORTALITY OF PATIENTS WITH AND WITHOUT A HISTORY OF INFANTILE ECZEMA

	Patients with					
	Eczema		*No eczema*		*Total*	
Dermatological history	*Number*	*Number of deaths*	*Number*	*Number of deaths*	*Number*	*Number of deaths*
Adequate.....	13	5	30	2	43	7
Inadequate....	3	0	52	8	55	8
Total.....	16	5	82	10	98	15

The percentage death rate amongst the phenylketonurics with infantile eczema was 31% compared with a mortality of 12% for the rest of the series. Using the absolute figures (Table IV), the difference is not significant ($x^2 = 2.27$; $n = 1$; $0.2 > p > 0.1$). The difference is significant if the analysis is confined to the 43 patients with an adequate dermatological history ($x^2 = 4.68$; $n = 1$; $0.05 > p > 0.02$).

SEX

There were 44 male and 54 female patients with phenylketonuria. There has been a slight excess of females in most reported series, which is attributed to a slightly higher death rate in male patients. The age and sex distribution of this series (Table II) shows a slightly higher ratio of females to males in the older age groups and is thus consistent with this explanation.

RACE

The first patients that Folling described with phenylketonuria were Norwegian.[18] Since then it has become clear that the disease is predominantly one of North Europeans and their descendants. Phenylketonuria is quite common among Italians but is rare in Jews.[2, 20, 21] Several cases have been reported from Japan[5, 22] but there are only single examples of patients of Mexican[3] or part-Spanish descent.[23] Phenylketonuria has been described in a Brazilian Negro,[24] a mulatto[25] and a child whose parents were Negro-white and Negro-Indian.[16]

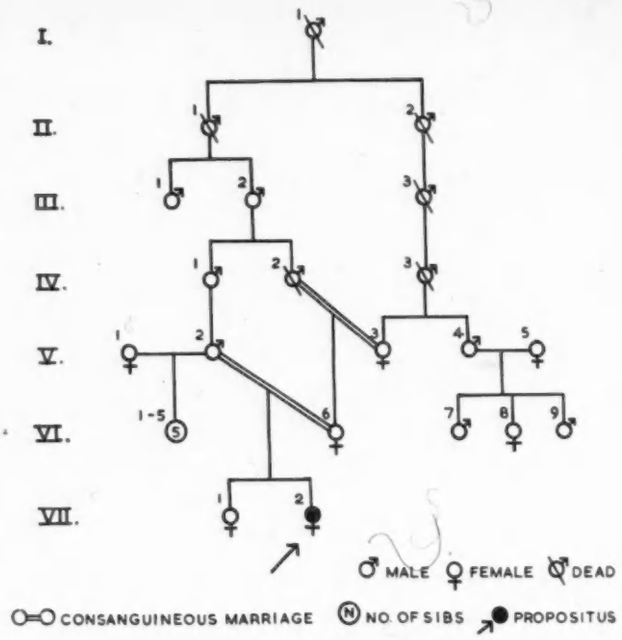

Fig. 3.—Pedigree of Myra B-C., the Ojibwa Indian.

This series conformed to a similar pattern. A racial background was recorded in some 50 families. In order of decreasing frequency these were said to be English, Irish, Scottish, French, Italian, Dutch, Polish and Russian. There were several mixed marriages between these groups and single Polish-German, Danish-English, Scottish-Ukrainian and Scottish-Syrian families. One child was a North American Indian and is apparently the first pure-blood Indian with phenylketonuria to be reported.

CASE REPORT

Myra B-C. was born on February 2, 1950. Her pedigree is shown in Fig. 3. She was apparently a pure-blood Ojibwa Indian. Her parents are first cousins and are further related by having a common ancestor four generations previously on the paternal side and five generations previously on the maternal side of the family. There was a history of diabetes mellitus on the maternal side.

She was born of a seven-months' pregnancy: delivery was normal and birth weight was 5 lb. 6 oz. (2.4 kg.). She was breast fed for three months without difficulty. Her development throughout infancy was slow, and she was given thyroid for one year from the age of 12 months. At 2 years of age she was restless and agitated, and was given phenobarbitone. This was withdrawn for a week at the age of 5 years and she had several major convulsions. Between the ages of 2 and 5 years she had four bouts of pneumonia. She was admitted to the Ontario Hospital School, Orillia, on January 30, 1956. Phenylketones were found in her urine by ferric chloride test on February 1, 1956.

Examination in 1960 (see Fig. 4) revealed a retarded child at the idiot level. She walked about the ward, was toilet-trained, fed herself and was easy to manage, but showed no evidence of speech. Her

TABLE V.—PHENYLKETONURIA: PERCENTAGE OF AFFECTED SIBS ESTIMATED BY WEINBERG'S "SIB METHOD"

Family	*s*	*t*	*t (s-1)*	*t (t-1)*	*Family*	*s*	*t*	*t (s-1)*	*t (t-1)*	*Family*	*s*	*t*	*t (s-1)*	*t (t-1)*
1	1	1	0	0	26	6	2	10	2	51	11	3	30	6
2	3	2	4	2	27	2	2	2	2	52	3	1	2	0
3	2	1	1	0	28	3	1	2	0	53	12	3	33	6
4	1	1	0	0	29	3	3	6	6	54	2	1	1	0
5	3	2	4	2	30	5	1	4	0	55	2	1	1	0
6	5	2	8	2	31	2	1	1	0	56	4	1	3	0
7	1	1	0	0	32	3	1	2	0	57	2	1	1	0
8	3	1	2	0	33	3	1	2	0	58	5	1	4	0
9	2	2	2	2	34	1	1	0	0	59	1	1	0	0
10	3	2	4	2	35	2	1	1	0	60	2	1	1	0
11	3	1	2	0	36	3	3	6	6	61	2	1	1	0
12	7	1	6	0	37	3	1	2	0	62	2	1	1	0
13	2	1	1	0	38	4	1	3	0	63	1	1	0	0
14	2	1	1	0	39	4	1	3	0	64	6	1	5	0
15	2	1	1	0	40	2	1	1	0	65	1	1	0	0
16	5	1	4	0	41	3	2	4	2	66	1	1	0	0
17	4	2	6	2	42	3	1	2	0	67	6	2	10	2
18	3	1	2	0	43	3	1	2	0	68	12	5	55	20
19	2	1	1	0	44	5	1	4	0	69	2	2	2	2
20	3	1	2	0	45	2	2	2	2					
21	1	1	0	0	46	2	1	1	0		232	95	292	72
22	4	2	6	2	47	4	2	6	2					
23	3	1	2	0	48	5	1	4	0					
24	3	1	2	0	49	4	1	3	0					
25	2	1	1	0	50	8	1	7	0					

$$P = \frac{\Sigma t(t-1)}{\Sigma t(s-1)} \times 100 = 24.65$$

$$\text{S.E.} = \sqrt{\frac{P(100-P)}{\Sigma s}}$$

$$= \pm 2.83$$

s = No. of sibs in each family.
t = No. of sibs with phenylketonuria.
P = estimated % of sibs with phenylketonuria.
S.E. = standard error of the estimate.

height was 48 in. (1.22 m.) and weight 66 lb. (30 kg.). Her head was somewhat pointed. Head circumference was 19 in. (48 cm.). She had very dark brown hair and dark brown irides. Her skin was medium brown; no eczema was present. There was early breast development. No abnormalities were detected on general physical examination. Her teeth were normally spaced.

Urine examination: phenylketones were detected by 10% ferric chloride test and Phenistix; no sugar present. Her fasting blood sugar level was 104 mg. %. A fasting plasma phenylalanine determination was 28.7 mg. %.

Fig. 4.—Phenylketonuria in an Ojibwa Indian girl.

Unfortunately, only the patient has been seen and examined. Two further members of the family (V, 4 and VI, 9) who are also retarded have had negative ferric chloride and Phenistix tests on the urine. The details of the family were obtained by the public health nurse for the reservation; an attempt is being made to find and examine the other members.

The pedigree shows the consanguineous marriages. The maternal grandfather (IV, 2) died at the age of 40 years from an accident in a sawmill. The maternal great-grandfather (IV, 3) and the maternal grandmother (V, 3) both suffer from diabetes mellitus. The maternal great uncle (V, 4) is said to be a low-grade moron who has had three children by a mentally defective girl (V, 5). Two out of these three children (VI, 8 and VI, 9) are said to be mentally defective.

GENETICS

Phenylketonuria is thought to be inherited as an autosomal recessive. If this is so, then the ratio of unaffected to affected sibs should be 3 to 1. In this series (excluding one family of three patients for reasons described later), 95 patients came from 69 sibships with a total of 232 sibs. This is a ratio of 137 unaffected to 95 affected sibs or about 1.4 to 1, which is a far greater proportion of affected sibs than expected on the recessive hypothesis. The reason is that those families that are potentially able to produce phenylketonuric children, but in fact produce only normal children, escape notice.

Various ways of allowing for this situation have been devised. Two different methods used by

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Jervis[2] and Munro[11] on somewhat similar case material in the United States and England, respectively, have been applied to the present series. In the first method (Table V), a correction is applied to each sibship throughout the series and the corrected percentage of affected sibs is compared to the expected 25%. In this case the corrected percentage worked out to be 24.65. The agreement is close and the difference between the observed and expected figures (0.35) is well within the standard error.

TABLE VI.—PHENYLKETONURIA: FACTORIAL METHOD FOR TESTING THE EXPECTED 3 TO 1 RATIO OF NORMAL TO AFFECTED SIBS[2, 11]

Size of sibship S	*No. of sibships of size S, N_s*	*Total No. of sibs, $S.N_s$*	*Number of sibs with phenylketonuria*		*Variance of No. expected $N_s.K_s$**
			Observed	*Expected**	
1	9	9	9	9.0	0.0
2	20	40	24	22.86	2.44
3	19	57	27	24.65	5.0
4	7	28	10	10.24	2.94
5	6	30	7	9.83	3.55
6	3	18	5	5.48	2.33
7	1	7	1	2.02	0.97
8	1	8	1	2.22	1.17
9	0	0	0	0.0	0.0
10	0	0	0	0.0	0.0
11	1	11	3	2.87	1.81
12	2	24	8	6.20	4.04
Total.....	69	232	95	95.37	24.25

Standard error = $\sqrt{24.25} = \pm 4.92$

* = Values given by Penrose.[13]

In the second method (Table VI), the *a priori* assumption is made that the ratio of unaffected to affected sibs is, in fact, 3 to 1. The theoretically expected frequency of cases is then calculated over the series for sibships of various sizes, and the expected number of affected cases compared with that actually observed. In this series the expected number of cases worked out to be 95.37. Ninety-five cases were in fact observed; the difference is again small and well within the standard error.

CONSANGUINITY

It is a characteristic of a recessively inherited condition that the frequency of consanguineous marriages amongst the parents of affected patients is greater than in the general population. The rate of consanguineous marriages in the general population is hard to estimate but in the United States (and probably in Canada) it is now thought to be less than 1%.[26] In this series, out of 69 marriages, 4 (or 5.8%) were between first cousins.

One female phenylketonuric was a twin; her co-twin was a normal boy. There were two sets of first cousins with phenylketonuria, but the total number of cousins for the series as a whole is not known. There was one family with two uncles, an aunt and a nephew with phenylketonuria, and one family (omitted from the estimation of the Mendelian ratios) in which a mother and two out of her three children all had phenylketonuria.

DISCUSSION

Since the 83 living patients in this series probably represent only one-third of Ontario's population of phenylketonuric individuals, it may be of interest to speculate on the whereabouts of the other two-thirds. There would seem to be four likely groups of patients. For this purpose, children and adults are considered separately.

Children

1. At home; not under medical care; not diagnosed. This is the most important group from the point of view of useful therapy. The problem of the early diagnosis of such cases is not easy. Mass screening tests for phenylketonuria have been advised and several are in progress.[27-29] Another useful approach would seem to be a high index of suspicion on the part of the doctors and nurses who care for children, together with facilities close at hand for testing the urine for phenylketonuria.[30]

2. At home; under medical care; may or may not be diagnosed. Such children might be found in doctors' offices, among the outpatients of pediatric hospitals, in schools for retarded children, at occupation centres, at neuroconvulsive clinics or at skin clinics with eczema or well-baby clinics with feeding problems.[9] The importance of diagnosis in this group is twofold. In the first place, treatment with a low phenylalanine diet may well alleviate eczema and seizures and, in some cases, prevent intellectual deterioration. In the second place, the discovery of a patient with phenylketonuria should immediately lead to testing of all present and future siblings and so to a really early diagnosis of other patients.

Adults

3. The Ontario Hospitals; may or may not be diagnosed. By this is meant mental hospitals as opposed to the Hospital Schools for retarded children. Two patients from this series are in this group. As a general rule, however, it seems unlikely that the adult psychotic population contains any large number of undiagnosed phenylketonurics.[5]

4. At home; may or may not be diagnosed. Three cases from this series fit into this group. The first two are sibs who live in a rural area. The brother, aged 36 years, can do little and has a disability pension. The sister, aged 28 years, does housework and helps look after children. Both patients are retarded but they have been raised in an undemanding environment and so have avoided hospitalization. By contrast, the third case, a woman of 36 years, lives in an urban area and can in no way be described as *suffering* from phenylketonuria. She is a bright and active housewife with an I.Q. of 102 who has had three children. One of her children is a 13-year-old girl with phenylketonuria who is in an Ontario Hospital School. One child is a normal schoolboy and the third is a four-month-old phenylketonuric patient on treatment with a

low phenylalanine diet. The proportion of untreated phenylketonurics who have normal intelligence is not yet known but, according to Knox,[1] is probably less than 5%.

The practical importance of case-finding in these last two groups is that, once more, it may lead to an early diagnosis in others.

The age distribution of the patients indicates that the mortality of untreated phenylketonuria is about the same as that of mental deficiency in general. This suggests that the biochemical lesion in phenylketonuria has no specific lethal effect except insofar as it causes mental deficiency. The immediate cause of death was attributed to a respiratory infection in over half the patients. Case 15 had a duodenal and perforated esophageal ulcer. One other phenylketonuric has been reported in the literature as dying from a perforated peptic ulcer.[5]

The present figures indicate that the mortality rate of phenylketonuric patients with a history of infantile eczema is higher than those with phenylketonuria alone. The whole relationship of phenylketonuria to eczema, and possibly other skin lesions, is of great interest and would clearly bear much further investigation. A recent paper failed to demonstrate any increased sensitivity of the phenylketonuric person's skin to ultraviolet light.[31]

The Indian patient with phenylketonuria had a brown skin and very dark brown hair and eyes. Several other patients had dark hair. This emphasizes the fact that, although phenylketonurics have lighter coloured hair than other members of their families,[32] fair hair and blue eyes are not essential to the clinical picture and are of little diagnostic value.

The close agreement between the observed and expected ratios of normal to affected sibs provides further evidence that phenylketonuria is transmitted as a Mendelian recessive. As Knox[5] points out, this lends considerable weight to estimates of the expected frequency of phenylketonuria in the relatives of known cases.[3] These estimates depend, first, on the assumption that phenylketonuria is recessively inherited and, second, on the incidence of the disease in the general population. The accuracy of these estimates could be increased by a precise knowledge of the incidence of phenylketonuria in the population concerned. Furthermore, the identification of the heterozygotes by means of phenylalanine loading tests[33] now seems a real possibility, at least in many cases, and this should improve the accuracy and value of eugenic advice.

SUMMARY

Details are given of the age, sex and racial distribution, geographic location and mortality of 98 patients with phenylketonuria from Ontario. By current estimates of the incidence of the disease, the 83 living patients in this series represent about one-third of the province's phenylketonuric population.

The age distribution of the patients suggests that untreated phenylketonuria has an increased mortality rate but that this is no higher than that associated with mental defect in general. There is some evidence that a history of infantile eczema worsens the prognosis.

Phenylketonuria is reported in an apparently pure-blood Ojibwa Indian.

The corrected ratio of patients affected with phenylketonuria to their unaffected sibs agreed closely with the ratio of 1 to 3 expected in a recessively inherited disorder.

The findings are discussed and suggestions put forward as to where the remainder of the cases in the province may be sought.

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PREMATURITY AND THE CONDUCT OF LABOUR*

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FROM THE figures quoted for the incidence of prematurity, it becomes obvious that the management of the premature infant has assumed a position of the greatest possible importance in the obstetrical thinking of today.

Maternal morbidity has been cut to an almost irreducible minimum by improved standards of prenatal care, improved surgical techniques, a better understanding of toxemia, antepartum hemorrhage, and the medical conditions associated with pregnancy, by improvement in blood transfusion services, an ever-widening spectrum of antibiotic drugs, and by countless other factors. Similarly, infant mortality figures have been lowered to a degree undreamed of but a few decades ago. The sobering fact remains that, with all these improvements proceeding along in a more or less orderly fashion, we have failed to keep pace in the field of prematurity.

What is the picture at the moment? A quarter of a million premature babies arrive annually in the United States and this figure has not dropped appreciably in the past decade.[9] Nine per cent of these prematures will not survive[8] and premature deaths account for at least half of all infant deaths in the neonatal period.[3, 8]

This somewhat bleak outlook is, in part at least, made to look brighter because of the continually increasing interest being focused on the prenatal and natal aspects of prematurity. To indicate their importance, Simpson and Geppert,[7] when speaking on prematurity, stated that "ninety per cent of fetal loss is attributed to prenatal and natal causes". If we are to decrease appreciably the loss of life from prematurity, we must in the final analysis learn more about the prevention of prematurity in the prenatal period. In the meantime, we have at our disposal the means and knowledge for substantially lowering the premature fetal loss in those cases where labour has already been established.

Any study such as this on the intranatal aspects of the premature inevitably leads to a consideration of the pathological findings which result in death. Lesions related to anoxia head the list by a large margin. In his review of 38 postmortem examinations on premature infants, Taylor[8] found that 19 infants (50%) died as the direct or indirect result of anoxia. Donald[1] in a more recent study at Hammersmith noted that asphyxia accounted for 83% of a series of 57 deaths in prematures.

Anoxia may manifest itself pathologically singly or in a combination of lesions. It now appears certain that intraventricular hemorrhage is the result of anoxia and not trauma, as was once thought. The hemorrhage commences as a diffuse capillary ooze from the subependymal vessels on the surface of the caudate nuclei,[2] and from there it subsequently ruptures through into the ventricular system with further embarrassment of an already anoxic respiratory centre. How much intrauterine anoxia enters into this mechanism as compared with anoxia in the immediate neonatal period in any given case may be impossible to determine, because either or both may have been present.

Atelectasis is another possible and important sequel to anoxia. We see atelectasis of the newborn far more commonly in premature than in mature infants, even where no obstruction to the airways is present, and as Donald has noted, "the surest defence against dying from atelectasis is vaginal delivery at term". This apparent inability of the premature infant to establish satisfactory respirations is at times the direct result of anoxia. The atelectatic lung will not permit of satisfactory oxygenation in the pulmonary circulation. This leads to further anoxia, and a vicious circle is established. That the prematurely born infant is particularly susceptible to anoxia has been adequately demonstrated by Taylor and his coworkers.[8] Their studies have shown that premature infants are, for a number of possible reasons, less able to oxygenate their arterial blood than are mature infants. This means, in effect, that prematurity predisposes the infant to anoxia. The anoxia may lead to atelectasis and the atelectasis, by improper pulmonary ventilation, contributes to the already precarious supply of oxygen.

The problem of hyaline membrane formation is far from settled, but there is accumulating evidence which indicates that it too is primarily the result rather than the cause of anoxia. In this condition, the eosinophilic membrane formation plugs the pulmonary alveoli, with a resultant failure of adequate pulmonary ventilation, and this in turn leads to an aggravation of the anoxic state. Whether this anoxia has its beginning during labour, during the immediate post-delivery period when the infant has difficulty in adequately oxygenating its arterial blood, or whether it is the sequel to atelectasis in which amniotic fluid and debris are aspirated and lead to the formation of the membrane, is once more open to question. Suffice it to say, however, that the chain of events would appear to have their beginnings in anoxia, and that hyaline membrane formation is a common pathological finding in the premature neonate.

The increasing awareness of the dangers of this fetal and neonatal anoxia has assisted in establishing a sound clinical approach for the intranatal period.

1. *Analgesia.*—The employment of little or no analgesic drug is stressed in all writings.

2. *Anesthesia.*—Inhalation anesthesia for delivery is known to produce a lowering of oxygen satura-

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tion in the fetus. In premature deliveries, therefore, where anoxia is known to be the major killer, general anesthesia is to be avoided whenever possible, and oxygen supplied by mask to the mother during delivery has a rational foundation.

3. *Vaginal delivery.*—Whenever a choice between vaginal and abdominal delivery of a premature infant presents, logical conservative obstetrics or even medical intuition might lead one to believe that any possible advantage would lie in favour of the natural process of birth. This assumption is amply substantiated by clinical experience. The premature fetus delivered by abdominal section may initially do better, but any immediate advantage to the infant is frequently more than offset by a higher neonatal loss among the babies delivered by Cesarean section.

Running second as a cause of premature death is injury to the infant, usually in the form of lacerations of the falx or tentorium. Injury is the cause of death in variously reported series in from 5 to 20% of cases. The general principles of management during the intranatal period that will minimize the possibility of injury are for the most part well known but all too often forgotten.

1. *Delivery of the head* in vertex presentations, in most cases, can be accomplished either spontaneously or by outlet forceps, provided always the utmost gentleness is employed, and the resistance of the perineum is relieved by a generous episiotomy. Spontaneous delivery is preferable, however, in those cases in which the fetal head is extended, where a very real danger of intracranial hemorrhage exists. On the other hand, in cases of tumultuous labour which might end precipitately, or in those cases where the second stage is prolonged and a possibility of brain damage is present from the effect of the infant's head pounding on the perineum, a low forceps operation is less traumatic than a spontaneous one.

2. *In breech presentation*, which is considerably more frequent in premature than in term deliveries, it must be recalled that, not infrequently, the cervix is somewhat less than fully dilated after delivery of the infant's body. For this reason, when the body and shoulders of the baby have been delivered, we prefer to allow the body to hang downwards, as advocated by Burns and Marshall in Liverpool, in order to produce gradual flexion of the head.

The sudden release of intracranial pressure which follows delivery of the head can result in brain damage in a premature infant. This danger exists in vertex presentations, but to an even greater extent in breech delivery. At all costs, the head must be delivered very slowly, and guided in such a way as to prevent its sudden expansion.

3. *Multiple births* account for approximately 16% of all prematures. Operative delivery of the second twin does not appear to prejudice its chances for survival[5] unless general anesthesia is required for the procedure.

Finally as a cause of premature infant death that at times might have been considered preventable by closer supervision, is sepsis. It is an established fact that prolonged labour in association with premature rupture of the membranes may result in an intrauterine infection with transplacental spread and fetal bacteremia. In a large percentage of the cases where no cause for the premature labour can be found, premature rupture of membranes, once again for causes unknown, is the initiating factor. The use of a small daily dosage of a wide-spectrum antibiotic from the time of rupture and during labour should combat any tendency towards fetal infection.

There are a few considerations in the management of premature labour and in the technique of delivery worthy of special mention. Immediately the head is born, it should be inclined downwards, except where intracranial damage is suspected. Not infrequently there appears to be unnecessary haste in getting the baby up on the patient's abdomen or in a cot. We make it a practice for the obstetrician to hold the baby on his knees, head downwards, and to strip the nose and trachea. The baby's first cry is the most important one it will ever make and for this reason it is essential that a mucus plug or bit of debris be prevented from being aspirated by the child's first gasp. The umbilical cord is palpated at a distance of approximately six to eight inches from the umbilicus and is not tied until pulsations have ceased, unless extenuating circumstances prevail. One wonders if this routine is not carried out, partly at least, to prevent unnecessary handling or suctioning by others present at the delivery.

In the management of premature labour, there may be some reluctance on the part of the attending physician to be constantly at hand during the period of active labour. All too often the care of this patient is delegated to others less well trained, with the result that the first indication that progress is being made is given by the patient announcing that the baby is being born. If we are to lessen the likelihood of anoxia and if we are to reduce the hazard of fetal injury in premature births, patients must be watched closely during the natal period.

The premature baby delivered by Cesarean section presents the additional problem that it often does poorly after what appears to be a good start. When the lower segment has been exposed in readiness for the uterine incision, the administration of ergot into the uterus at that time, rather than after delivery of the placenta, may provide additional needed blood for the infant. Rapid stripping of the umbilical cord as advocated by Siddall, Crissey and Knapp[6] has been shown to raise significantly the infant's hemoglobin level and is certainly worthy of serious consideration when dealing with the premature. Gastric suction should be employed when feasible or whenever the infant's respirations are poor. In premature babies delivered by Ces-

arean section, too little attention is devoted to posturing the baby immediately after it is born. Surely this child is deserving of the treatment meted out to a premature delivered per vaginam.

From an obstetrical point of view, where does our responsibility end? When ideal circumstances prevail, our attention can be turned away from the baby from the moment the cord is cut and the child placed in a preheated incubator or cot. From this moment onwards the child's welfare will be the responsibility of the pediatrician present at the time of delivery.

Because the prevailing conditions at the moment of birth are frequently somewhat less than ideal, it becomes imperative that the physician in charge of delivery be equipped with the knowledge and skill necessary for the care of the premature infant in the immediate neonatal period.

The child who cries vigorously within a minute or two of birth, or one in whom spontaneous rhythmic respirations are established within this period of time, presents little or no problem. Directly the cord is cut, the baby is immediately placed with its head inclined downwards in a preheated incubator into which an oxygen flow of two or three litres per minute is maintained.

It is when the condition of the premature infant is not satisfactory that difficulties begin and confusion as to the best methods of treatment arise. Much has been said and written on this subject, about the criteria of an asphyxiated baby, about the need or lack of it for resuscitation, and if resuscitation is required in the immediate neonatal period, what method or methods are helpful. Two groups of infants require separate consideration:

1. In the first group, the infant either does not cry or its respirations are not properly established within two minutes of birth. It is our belief that this baby requires suctioning of the trachea and possibly assistance from the resuscitator. For the most part, this assistance, when required, takes the form of putting the machine on the inhalator and supplying 100% oxygen by mask to the infant. The resuscitator itself need be resorted to only if the child becomes apneic. As soon as the respirations have become rhythmic, or a vigorous cry is heard from the infant, it is immediately placed in the incubator and the procedure now follows the same lines as those adopted for the apparently well child at birth.

2. The second group is made up of those infants apneic at birth, but with some detectable cardiac action. These by definition we would refer to as "apparently dead", as opposed to the previous group to which the term "apparently dying" would apply. The apneic baby requires immediate tracheal catheterization, using a Magill polyethylene No. 0 or 00 catheter. The catheter, after use in suctioning to remove any obstructive material, is left in the trachea, and assisted respirations are maintained by means of a biphasic type of resuscitator until such time as the infant establishes satisfactory respirations of his own, or until all hope for the child must be abandoned.

Damage to the baby's upper respiratory passage from tracheal catheterization will cease to be a real danger only when all of us learn how to carry out this procedure easily and gently. The smaller the baby, the greater the need for gentleness. So far as the resuscitator is concerned, many authorities condemn its use in the resuscitation of the premature infant. One inescapable fact remains, however, and that is that the baby who is either breathing inadequately or not at all must be provided with oxygen by some form of assisted respiration. The positive-negative type of resuscitator would seem to be a safe means of providing this and its use should be omitted only if and when a safe and more effective alternative becomes available.

SUMMARY AND CONCLUSIONS

Salvage of the premature baby lags behind that of the full-term infant. There is a constant loss of 10% of the 250,000 prematures born yearly in the United States. Reduction of this number offers one of the great challenges in modern obstetrics, because here occurs 50% of all infant deaths.

Salvage, previously limited to the neonatal period, must begin earlier and become the responsibility of the obstetrician.

Anoxia, cerebral trauma and sepsis are the major causes of fetal wastage during the natal period.

Anoxia with its associated sequelae of atelectasis, hyaline membrane disease, and cerebral hemorrhage are best prevented by minimal analgesia, thoughtfully administered anesthesia, gentle and slow vaginal delivery, with use of episiotomy and outlet forceps when indicated. The factors proven to increase the hazards of anoxia include Cesarean section, precipitate delivery, and faulty management of the second twin.

Cerebral trauma is largely preventable by gentleness in spontaneous delivery, a generous episiotomy, and the use of "slow-down" forceps in precipitate delivery. In breech delivery the Burns-Marshall maneuver and slow delivery of the head are advocated.

The prevention of fetal sepsis where rupture of the membranes has occurred begins before birth, with the administration of antibiotics to the mother.

After delivery, care of the premature depends upon the presence or absence of respiratory effort. Where this is present even to a poor degree, oxygenation, warmth and minimal handling suffice. Where apnea is present, tracheal suction followed by mechanical resuscitation is advocated.

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DISEASES IN NATURE COMMUNICABLE TO MAN*

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METHODS OF SPREAD OF THE ZOONOSES

ALTHOUGH many common bacterial and viral infections of man are contracted solely by close exposure to infected humans who are excreting organisms into the environment through the respiratory, genitourinary or gastrointestinal tracts, or from inflamed conjunctivae or open skin lesions, there is a group of diseases termed the zoonoses in which the infective agent is transmitted to man from a mammalian or avian reservoir in nature. There are two principal means (Table I) by which micro-organisms may be transmitted from animals to man: (1) by direct transfer and (2) by the bite of an arthropod vector. Those bacterial diseases which are spread directly from animals to man include brucellosis, plague, tularemia and leptospirosis, whilst rickettsial and viral diseases such as Q fever, ornithosis, rabies and B virus reach human hosts by this method. Arthropod vectors are essential for the transmission of viral and rickettsial diseases including the encephalitides, Colorado tick fever, Rocky Mountain spotted fever, and in special circumstances Q fever also, but in addition they may provide an alternative mechanism by which bacterial diseases such as plague and tularemia may be transmitted to man.

TABLE I.—METHODS OF SPREAD OF COMMONLY OCCURRING ZOONOSES IN CANADA

Direct			*Arthropod Vector*		
Inhalation	*Ingestion*	*Skin abrasion*	*Tick*	*Mosquito*	*Flea*
Brucellosis	Brucellosis	Brucellosis	Tularemia	Western equine encephalomyelitis	Plague
Q fever	Q fever	Plague	Rocky Mountain spotted fever		
Ornithosis	Leptospirosis	Tularemia	Q fever		
		Leptospirosis	Powassan		
		Rabies	Colorado tick fever		
		B virus			

For direct transfer of organisms to take place between animals and man, large numbers of organisms must reach the exterior following multiplication in the animal host, by way of the mouth, the urine, the feces, the milk or the products of conception, or they must be present in high titre in various tissues of the body. Organisms excreted through the alimentary or genitourinary tracts may become mixed with dust which is inhaled by other animals or man, as in the case of brucellosis, Q fever and ornithosis for example. Brucella and Q fever organisms which are excreted in milk may be transferred to man by ingestion of unpasteurized milk. Man becomes especially liable to infection with plague and tularemia during the skinning of infected rabbits or rodents captured in the field, since these organisms are present in high titre in animal tissues and they may gain ready access to human tissues through minute skin abrasions. Leptospirae are regularly excreted in urine of infected domestic animals such as dogs and cattle, so that a dairy farmer may contract infection through abrasions in his feet while working barefooted around his milking shed or pastures. Rabies virus is commonly excreted in the saliva of infected animals, gaining access to the tissues of the new host by animal bite. In India, rabies developed in 19 of 44 unvaccinated persons who were bitten by animals which were proved rabid subsequently.[1] Laboratory workers may contract infection with B virus following bite by infected monkeys or contact of abraded skin with supernatant fluids of tissue cultures of monkey kidney cells.[2, 3]

In diseases transmitted by mosquitoes or ticks, a period of extrinsic incubation, during which virus ingested during a blood meal multiplies in arthropod tissue and localizes in the salivary glands, must elapse before the arthropod becomes capable of transmitting virus by biting a new host. In the case of plague and murine typhus which are transmitted by fleas, the organisms multiply in the tissues of the flea following ingestion of an infective blood meal and subsequently organisms are excreted in flea feces. Owing to the irritant nature of flea bites, organisms may be introduced readily into mammalian tissues by scratching. While sylvatic plague is normally maintained in nature by a cycle involving rodents and fleas, the only human case of plague reported in Canada was contracted through a small knife wound sustained while skinning infected mink.[4]

CLINICAL RECOGNITION OF THE ZOONOSES

The presenting symptom in most cases of human infection with one of the zoonoses is fever which may have persisted for days to weeks after a fairly sudden onset. Although physical examination frequently reveals no abnormality apart from elevated temperature, a search for an eschar, after a recent tick bite or a local lesion surrounding a bite or cut through which organisms gained access to the body, should always be undertaken. In the case of tula-

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remia and plague, the regional lymph nodes are frequently enlarged and they may suppurate. Usually the most important clues to diagnosis are obtained from the history. For example, repeated exposure to sick psittacine birds in the home or employment at a turkey slaughterhouse may suggest ornithosis; exposure to sheep during lambing may point to Q fever; employment at a meat packing plant may suggest Q fever or brucellosis; exposure to tick or mosquito bite in certain geographical zones may suggest encephalitis due to an arbor virus; and skinning of wild rabbits in certain areas may point to tularemia.

LABORATORY DIAGNOSIS

Virological and bacteriological laboratories may be of considerable assistance in the etiological diagnosis of the zoonoses. In the case of the bacterial zoonoses (Table II), attempts to culture the organism from blood, local lesions or suppurative lymph nodes should always be undertaken. (Should a patient die, portions of liver, spleen, lungs and sometimes bone marrow should be cultured.) Serological procedures, although of considerable assistance in confirming the results of bacterial isolations, are of limited value as a sole means of diagnosis in individual cases, but they are of extreme value in epidemiological surveys for the prevalence of certain bacterial pathogens in a given region.

The laboratory diagnosis of virus infections[5] employs both direct (isolation) and indirect (serological) tests. Direct tests include (a) demonstration of virus particles (elementary bodies) or their aggregates (inclusion bodies) by microscopic study of stained smears of diseased tissue such as brain or conjunctival scrapings, and (b) cultivation of the agent from tissues, blood, cerebrospinal fluid, feces or other excreta by inoculation of appropriate animals or tissue cultures. Wherever possible, the virologist attempts to isolate virus from the patient. Indirect tests are those in which an attempt is made to demonstrate an increase in the level of antibody to a particular virus in successive samples of the patient's serum. The three tests most frequently employed for detection of antibody are neutralization (NT), complement fixation (CF) and hemagglutination inhibition (HI). A fourfold or greater increase in the level of antibody between acute phase and convalescent phase sera provides good presumptive evidence of recent infection with the virus in question.

Among the viral and rickettsial zoonoses which have caused human disease in Canada (Table III), a laboratory diagnosis of infection with rabies virus may be made immediately at autopsy by demonstration of Negri bodies in the cytoplasm of neurones of the hippocampus. Isolation of virus from the brain of fatal cases of encephalitis should always be attempted by inoculation of a brain suspension intracerebrally into newborn mice and into tissue cultures of monkey kidney or human amnion cells. Frequently agents may be isolated from the blood of patients with Rocky Mountain spotted fever and Colorado tick fever, and infrequently from patients with Q fever. The sputum from cases of ornithosis may sometimes yield a virus by inoculation of eggs or weaned mice. The serological test of greatest value in diagnosis, apart from infections with rabies and B virus which uniformly terminate fatally, is the complement fixation test. For the rickettsiae and ornithosis this is the only test readily available, but the neutralization or hemagglutination tests may also be used in the diagnosis of infections with arbor viruses excepting Colorado tick fever for which no hemagglutinin is available.

TABLE II.—BACTERIAL ZOONOSES: DIAGNOSTIC PROCEDURES

Disease	*Distribution*	*Exposure to animals*	*Salient clinical features*	*Bacterial isolation*	*Serology*
Brucellosis	Canada-wide	Cattle, goats, swine	Fever	Blood	Agglutination
Plague	Alberta, Saskatchewan	Wild rodents, mink	Fever, bubo	Blood, bubo	Agglutination
Tularemia	Canada-wide	Lagomorphs	Fever, local lesion	Blood, local lesion	Agglutination
Leptospirosis	Canada-wide	Cattle, rodents	Fever, hemoglobinuria	Blood	Agglutination

TULAREMIA

Over 150 human cases of tularemia have been reported in Canada up to 1959[6] and this disease has occurred in every province. Between 1931 and 1944, 40 human cases of tularemia, 21 of which were attributed to rabbits, occurred in Alberta,[7] a concentration of cases occurring both in southern Alberta and around Edmonton. During 1960, two cases occurred in Alberta and six were reported from Ontario.[6]

There are two epidemiological patterns of tularemia in North America:[8] (1) tick-borne tularemia of rabbits, order Lagomorpha, which frequently affects other animals, may be transmitted by other arthropods, and is the source of 90% of human infections; (2) water-borne tularemia of true rodents, order Rodentia, which also affects other animals, and is the source of 5 to 10% of human infections (see Table IV).

In tick-borne tularemia of lagomorphs, the common reservoirs are cottontail rabbits, *Sylvilagus spp.*,[9] but snowshoe hares, *Lepus americanus*, and jack rabbits, *Lepus spp.*, may act as reservoirs in certain areas. The disease is highly fatal for cottontails, but less highly pathogenic for snowshoe hares. The tick species involved in transmitting tularemia

TABLE III.—VIRAL ZOONOSES: DIAGNOSTIC PROCEDURES

Disease	*Distribution*	*Exposure to animals*	*Salient clinical features*	*Virus isolation*		*Antibody test**
				Specimen	*Test system*	
Q fever	Quebec, western Ontario, prairie provinces	Sheep	Fever of unknown origin	Blood	Guinea pig	CF
Ornithosis	Canada-wide	Turkeys, psittacine birds	Fever of unknown origin, pneumonitis	Blood, sputum	Mouse, egg	CF
Rocky Mountain spotted fever	Saskatchewan, Alberta, British Columbia	Ticks	Spotted fever	Blood	Guinea pig	CF
Rabies	Canada-wide	Foxes, skunks	Fever, rages	Brain	Negri bodies in mice	nil
B virus	Laboratories	Monkeys	Encephalitis	Brain	Mice, tissue culture	NT
Western equine encephalomyelitis	Manitoba, Saskatchewan	Mosquitoes	Encephalitis	Brain	Suckling mice	CF, NT, HI
Powassan	Northern Ont.	Ticks	Encephalitis	Brain	Suckling mice	CF, NT, HI
Colorado tick fever	Western United States	Ticks	Fever	Blood	Suckling mice	CF, NT

*CF—complement fixation NT—neutralization HI—hemagglutination inhibition

amongst rabbits are principally *Dermacentor andersoni* in the Rocky Mountain region of western U.S.A. and Canada and *D. variabilis* elsewhere in U.S.A. However, the snowshoe hare tick, *Haemaphysalis leporis-palustris* (H.L.P.), may also be a vector, especially in northern Alberta. In northern Ontario H.L.P. is the dominant tick species and *Lepus americanus* is the only species of Lagomorph present. Man may become infected by the bite of an infective tick, usually *D. andersoni* or *D. variabilis*, since H.L.P. ticks attack man very rarely, or more commonly through small skin wounds which occur during skinning of infected rabbits. Sheep may also become infected while grazing in sagebrush areas heavily infested with *D. andersoni* ticks, but human infection has been contracted most infrequently through skinning dead sheep.[8] The sheep appear to play little part in maintaining the natural cycle of infection. Tularemia may also infect grouse, and the organism has been cultured both from tissues of dead or killed sage grouse, and from the tick species *Haemaphysalis cinnibarina* with which they were infested.

In water-borne tularemia of rodents, principal reservoirs include field mice *Microtus spp.*, muskrats *Ondatra spp.* and beaver *Castor canadensis*. Strains of *P. tularensis* recovered from dead or killed rodents and from nearby water in streams and lakes have a lower virulence for man and rabbits than the rabbit strain. Human infections may occur after ingestion of contaminated water or through skin wounds sustained during skinning of infected muskrats. Recently an epizootic of tularemia was encountered in muskrats (*O. zibethica*) in the Castor swamp in eastern Ontario, 35 miles south of Ottawa.[10]

TABLE IV.—BACTERIAL ZOONOSES: CHAINS OF INFECTION FROM NATURE TO MAN

Disease	*Animal reservoirs*	*Source of bacteria*	*Portal of entry into human*
Brucellosis	Cattle, goats, swine	Placenta, milk, carcass	Respiratory, gastrointestinal
Plague	Wild rodents, mink	Carcass, flea	Abraded skin
Tularemia	Lagomorphs, rodents	Carcass, water, tick	Abraded skin
Leptospirosis	Cattle, rodents	Carcass, water	Abraded skin, gastrointestinal

Q FEVER

Apart from an outbreak of Q fever which affected 62 employees of an abattoir at Princeville, Quebec, during April 1956,[11] only occasional cases have been reported elsewhere in Canada. Q fever may spread by the following three methods:[12] (1) most commonly by inhalation of organisms excreted in high titre in placentae and birth fluids, and to a lesser extent by ingestion of raw milk, thus resembl-

TABLE V.—VIRAL ZOONOSES: CHAINS OF INFECTION FROM NATURE TO MAN

Disease	*Animal reservoirs*	*Source of virus*	*Portal of entry into human*
Q fever	Cattle, sheep, goats	Placenta, milk	Respiratory, gastrointestinal
Ornithosis	Turkeys, psittacine birds	Carcass, feces	Respiratory
Rocky Mtn. spotted fever	Wild rodents	*D. andersoni* ticks	Tick bite
Rabies	Foxes, skunks	Saliva	Puncture wound of skin
B virus	Monkeys	Saliva	Puncture wound of skin
Western equine encephalitis	Wild birds	*C. tarsalis* mosquitoes	Mosquito bite
Powassan virus	Wild rodents	Ixodid ticks (?)	Tick bite
Colorado tick fever	Wild rodents	*D. andersoni* ticks	Tick bite

ing the mode of transmission of brucellosis; (2) by inhalation of organisms excreted in sputum from cases of pneumonitis or during autopsy on a fatal human case;[13] (3) by cycles involving ticks and bandicoots or rodents (see Table V). After its recognition as the causative agent of a febrile disease of slaughterhouse workers in Queensland, Australia, in 1935,[14] several outbreaks similar to that described by Topping *et al.*[15] have affected employees of abattoirs who are actually exposed to carcasses and offal, such as slaughterers and truck drivers who collect the carcasses. On dairy farms of southern California, where milking cows are held in the same paddocks as parturient cows,[16] over 10% of cattle had serological evidence of Q fever. Humans became infected principally by inhalation of enormous numbers of infective particles excreted in placentae,[17] and to a minor extent only by ingestion of raw milk which contained viable rickettsiae.[18] However, in northern California[19] and in Kent, England,[20] exposure to sheep especially during the lambing season was associated with an increased incidence of human cases of Q fever. In a recent survey of 200 dairy cattle herds in western Ontario,[21] 60 cows distributed through 14 herds had evidence of infection with Q fever. Sheep or goats were not grazed with these cattle. No illness suggestive of Q fever was encountered amongst the dairy farmers or their families.

The following two case histories[22] illustrate the principle of diagnosis of Q fever infection by suspecting its occurrence. During mid-April 1960 two children living on a farm 30 miles north-west of Toronto, close to an area in which dairy cattle had Q fever antibodies, became exposed to some sheep which had a febrile illness attributed to ticks. One week beforehand, the index case had a sore throat followed by a scarlatiniform rash. One week after exposure to the sheep, this patient developed anaphylactoid purpura which required hospitalization. Symptoms subsided after treatment by bed rest and penicillin. A serum sample taken on discharge from hospital, two weeks after exposure to sheep, had a Q fever antibody titre of 4. About three weeks after exposure to sheep the index case suddenly developed fever, severe frontal headache, pains in her limbs and a slight sore throat. Symptoms subsided within 24 hours after administration of chloramphenicol. Two weeks after this second febrile episode the Q fever antibody titre had risen to 16, and serum taken the next week showed titre 32. A younger sister developed a less severe febrile upset two weeks after exposure to the sheep and this illness persisted for about 10 days. Serum which was obtained from this patient three weeks after recovery (six weeks after exposure to sheep) had a Q fever antibody titre of 32. The rising or elevated Q fever antibody titres strongly suggested infection by *Coxiella burnetii* as the cause of their illnesses.

RABIES

Although rabies has been reported in animals throughout Canada on many occasions, its incidence amongst wildlife, especially foxes, and domestic animals, especially cattle, reached alarming proportions in the Province of Ontario during the 1958-59 winter with a peak incidence of more than 600 rabid animals in December 1958.[23] During 1959 the incidence of rabid animals declined, and this decline has continued through 1960. Despite the lower total number of rabid animals, the proportion of rabid skunks has increased from 4% in 1958 to 25% in 1960, while another important natural reservoir, the fox, has maintained about the same proportion of infected animals throughout. The skunk has now become an important natural reservoir, similar to conditions which prevail in the mid-western states, Texas and California.[24]

During September 1959, a child who lived 45 miles north-east of Toronto was bitten on the left index finger by a skunk near his home.[25] Almost four weeks later he complained of a burning sensation and hyperalgesia over the trunk, followed by shooting pains in the arms and trunk and weakness of the right shoulder musculature 10 days later. Cerebrospinal fluid contained 2 lymphocytes per c.mm., and sugar and protein levels were normal. Two days later he experienced several episodes of mental confusion lasting several minutes, accompanied by violent muscular activity and a shrill voice. These convulsive seizures recurred frequently until terminated by death four days later. He was comatose for the last two days antemortem. Touch preparations of the hippocampal uncus revealed numerous Negri bodies when stained by Sellers' technique, thus confirming the diagnosis of rabies immediately. In addition, perivascular cuffing by lymphocytes and aggregates of microglia, which are features typical of viral encephalitis, were found throughout the central nervous system. Rabies virus was isolated from the hippocampus, cerebral hemisphere and submandibular salivary gland obtained post mortem, and from two samples of saliva obtained ante mortem, by inoculation of newborn and weaned mice.

Rabid skunks frequently attack humans, whereas normal skunks usually run away from man. The incidence of skunk rabies in the vicinity of the home of our index case was the highest in Ontario, and rabid skunks have been obtained from this and other districts during 1960.[23] The skunk therefore is an important vector of rabies for man.

POWASSAN VIRUS

During September 1958, a child who lived on a farm at Powassan, Ontario, 200 miles north of Toronto, suddenly developed two mild convulsive seizures. Apart from a diffusely abnormal electroencephalogram, he remained asymptomatic until the third day when he became febrile, developed a stiff neck and showed 150 cells (60% lymphocytes)

in the cerebrospinal fluid. His level of consciousness decreased steadily, and he developed intermittent twitching of the right arm and a left-sided spastic hemiplegia. Breathing ceased the next day. Despite artificial respiration he died six days after onset of illness. Throughout the central nervous system, features typical of an acute viral encephalitis were seen, including perivascular cuffing, neuronophagia and foci of microglia. A virus, now termed Powassan virus,[26] was isolated from portions of the midbrain, cerebral cortex and cerebellum by inoculation of newborn and weaned mice. This virus was serologically related to, but distinct from, the virus of Russian spring-summer encephalitis.[27] Since the latter virus is transmitted readily by ticks, we postulated that Powassan virus may be tick-borne.

Serological surveys of human residents of northern Ontario showed antibody to Powassan virus in 1 of 6 family contacts, 2 of 65 residents of the adjacent community of North Bay and 3 of 52 Manitoulin Island residents.[28] These findings have been confirmed after subsequent serological surveys.[29] In the Powassan area, 5 of 23 chipmunks and 2 of 14 red squirrels had antibody to Powassan virus,[29] but antibody was not detected in 17 snowshoe hares, 21 farm animals or 15 birds. All hares captured were heavily infested with H.L.P. ticks, but the only man-biting ticks, *Ixodes angustus*, were found on two squirrels. On Manitoulin Island during the summer of 1960, Powassan antibody was detected in 5 of 178 snowshoe hares, 2 of 16 chipmunks and 3 of 56 squirrels. *Ixodes angustus* ticks were found occasionally on squirrels. From these observations we postulate that a cycle of infection occurs in nature between small forest fauna and ticks. Occasionally, infected ticks may transfer Powassan virus to snowshoe hares or humans who traverse tick-infested country, or who skin recently captured squirrels and chipmunks. We found that our index case frequently used to skin his newly shot ground game.

SUMMARY

The ecology of several of the more important diseases in nature communicable to man (zoonoses) which occur in Canada has been discussed from the standpoint of the route by which man may become infected. Diagnostic procedures which are applicable both to bacterial and viral zoonoses have been mentioned and their use has been exemplified by reference to tularemia, Q fever, rabies and encephalitis.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

MEDICAL INSPECTION OF SCHOOLS: REPORT TO THE CANADIAN MEDICAL ASSOCIATION

During recent years and in almost all civilized countries there has been a steadily increasing conviction that no system of education is complete which does not provide for medical inspection and supervision of schools and school children. All the great writers on education of modern times lay stress on the importance of bodily health and vigour, and, in their various systems, make provision for physical training and school hygiene.

Early in the seventeenth century Comenius, generally regarded as the father of modern education, made physical training a prominent part of his plan, and showed the advantage and necessity of airy school rooms and pleasant playgrounds. Towards the close of the same century, John Locke published his well known "Thoughts Concerning Education", in which he laid down minute rules for the physical exercise, diet, and regimen of the school boy.

Near the end of the eighteenth century, J. P. Frank, in Austria, made a study of school furniture and hygiene, and suggested a scheme of medical supervision, and it may be noticed that "as far as primary schools are concerned, Austria was the first country to publish effective legislation. A ministerial decree of 1873 ordered the establishment of permanent health committees, with physicians as regular members."

The activity of smaller countries is notable. Sweden has always had an honourable place. This, no doubt, is due to Ling, who studied medicine with the idea of organizing a scientific system of physical training. His system was adopted by the Swedish government in 1813, and the Central Gymnastic Institution, Stockholm, which has had so great an influence on physical education, was founded.

The first medical man to make a thorough study of school hygiene was Lorinser, in Germany, whose tract on the protection of health in schools was published in 1836.—John Stewart, *Canadian Medical Association Journal*, 1: 425, May 1911.

RESULTS OF TREATMENT OF MALIGNANT NEOPLASTIC DISEASE WITH RADIOACTIVE COLLOIDAL GOLD (Au^{198})
AN ANALYSIS OF 60 CASES*

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FOR THE past six years radioactive colloidal gold has been in use in the University Hospital, Edmonton, to attempt control of recurrent malignant effusions in serous cavities, and to irradiate prostatic carcinoma *in situ* and a variety of other conditions.

Historically, radioactive gold (Au^{198}) was first administered intraperitoneally by Hahn and his co-workers in 1947.[3] Since then a large number of reports have been published on the control of ascites and pleural effusions after administration of gold. Most workers appear to obtain 30 to 75% satisfactory results. Hahn estimated in 1947 that 80% of the production of gold from Oak Ridge in the United States and Harwell in England was used for this purpose, to the probable extent of 10,000 patients annually. At present the estimated figure for Canada lies between 300 and 350 patients per year.

It was found experimentally in 1947 that when colloidal gold was injected into the peritoneal cavity it remained there (owing to particle size), and was distributed evenly, chiefly over the walls of the abdominal cavity and partly in suspension in the fluid. These are two very important properties of the colloid, as it is undesirable to have the gold absorbed into the general blood stream and hence subject the patient to a significant total body radiation dose. It is also highly desirable not to have an uneven accumulation of the gold which might lead to local radiation necrosis. The whole radiation dose can be delivered in a reasonable time owing to the short half-life of this element and the radiation is confined (apart from the gamma component) to the walls of the cavity and to the floating cells. There are no toxic after-effects from the gold and, unlike radium, nothing has to be removed from the body when the required dose has been delivered. The whole body dose from the gamma component is small.

Flocks and his co-workers in 1951 were amongst the earliest users of Au^{198} in the treatment of carcinoma of the prostate. It had already been demonstrated that a striking reduction in tumour mass could be achieved by means of local implantation of radium or radon seeds, but, as in the case of external therapy, complications arose from high local doses to the bladder and bowel. Au^{198} presented many characteristics favourable for the treatment of carcinoma of the prostate. The gold remained at the site of injection in the tissue, was non-toxic, and had a suitably short half-life and energetic beta radiation which could deliver a massive highly localized dose to the tissue. This dose has been estimated as being between 7000 and 110,000 rep/c.c. of tumour tissue for complete decay, assuming ideal distribution.

The prophylactic use of Au^{198} after operation for ovarian cancer has been proposed by Keetel and others in order to irradiate malignant cells spilled in the peritoneal cavity and to try to prevent formation of ascitic fluid. It is recommended that the gold be instilled either at operation or as soon as possible afterwards and be accompanied by sufficient saline to ensure good distribution over the cavity walls. Andrews and associates estimated that the radiation from 100 mc. of Au^{198} (intraperitoneal) is in the order of 3000 rep per sq. cm. surface dose for complete decay.

METHODS

Au^{198} is available in Canada under Atomic Energy Commission licence from Charles E. Frosst & Co. and is a product of the nuclear reactor at Chalk River, Ontario.

Radioactive gold is an artificial isotope with a half-life of 2.69 days and its radiation consists chiefly of 0.97 Mev beta, and 0.411 Mev gamma rays. For clinical use it is prepared in sterile colloidal solution of high specific activity and consists of particle sizes ranging from 0.003 to 0.007 microns (μ) in diameter. It is pyrogen-free with a pH between 5.5 and 6.5. The natural colour of the colloid is deep cherry red. The colloidal gold may be diluted with water, saline and certain other non-metallic diluents. It does not ionize appreciably under normal conditions, and it is known to remain relatively biologically inert. The average beta radiation from this isotope is absorbed in under 1 mm. of tissue. The maximum penetration is 3.8 mm. Hence the beta radiation to tissue is highly localized. The gamma emission associated with the decay is not thought to add much to the effectiveness of the therapy, but is useful as a means of checking the distribution of the gold in the patient by external counting or scintillation scanning.

Each isotope centre evolves its own method of instillation of radioactive gold. The actual device used for administration is not important, as they all attempt to reduce the radiation exposure to the personnel from the source by shielding, to shorten the time for flow of the gold from source to patient and to decrease the likelihood of a radioactive spill during the procedure. The equipment developed by Simon[6] is generally recommended as highly efficient. The chief concern in the actual instillation into the patient's body (especially in intraperitoneal

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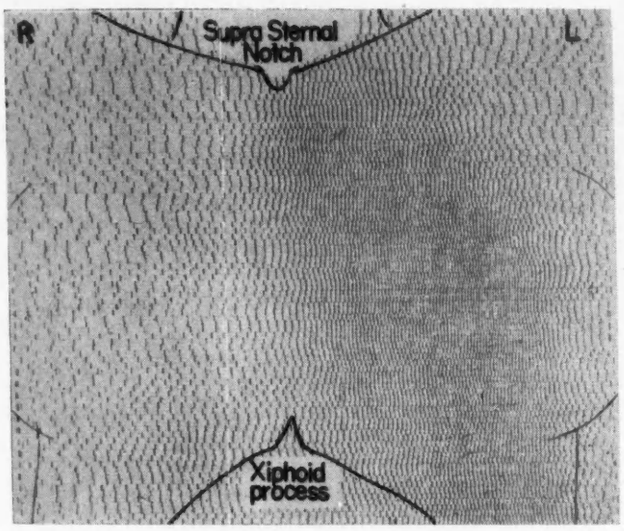

Fig. 1.—Typical scan obtained several days after the instillation of Au^{198} into left pleural cavity, showing excellent even distribution.

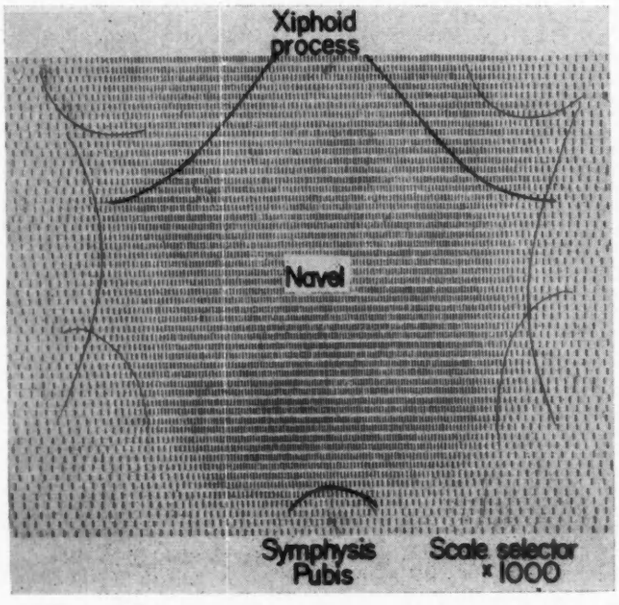

Fig. 2.—Typical scan obtained several days after the instillation of Au^{198} into the peritoneal cavity, showing good distribution of activity.

cases) is to be sure that the gold is placed truly in the cavity. This can sometimes prove rather difficult. Use may be made of a drainage catheter left in place after the operation (which must then be clamped off or removed after administration of the gold).

In the cases of intraperitoneal and intrapleural instillation of gold, if fluid is present in the abdominal or thoracic cavities, it is generally removed, at least partially, before the gold is instilled. If there is no fluid, then saline is introduced into the cavity to help distribute the gold within the body.

Once the gold is instilled the patient should be encouraged to move from side to side for about three hours to ensure an even distribution of radioactive particles. It is thought that about 80% of the dose is attached to the cavity walls at the end of this period of time.

External measurement with a survey meter or a scintillation scanner is used to check the distribution of activity (see Figs. 1 and 2). Our measurements of the level of radioactivity in blood, stool and urine after the instillation of Au^{198} have always been in close agreement with those given by Andrews;[1] that is, 0.04% of the total dose per day was found to be excreted in the urine, negligible amounts in the stool and up to 0.30 μc. per c.c. of plasma up to two weeks after injection.

In the case of carcinoma of the prostate the retropubic approach of Kerr *et al.*[4] was used.

For cystic brain tumours, the cystic contents were aspirated as far as possible at operation and gold was introduced in such concentration as to give approximately 10,000 rads to the inner surface of the cyst.

DOSAGE

The average dosage in millicuries (mc.) commonly quoted in the literature is 75 mc. to 150 mc. for the abdomen (not exceeding 150 mc. per single treatment) and 35 mc. to 75 mc. for the chest (not exceeding 120 mc. per treatment). In all cases the patients are hospitalized until the dose in the body has decayed to less than 30 mc.

All cases, except two, treated in the University Hospital, Edmonton, were proven pathologically to be malignant. The average amounts used in our series were as follows:

Carcinoma of the ovary with fluid	—abdomen	139 mc.
	—chest	70 mc.
Carcinoma of the breast with fluid	—abdomen	126 mc.
	—chest	77 mc.
Carcinoma of the bronchus	—chest	77 mc.
Carcinoma of the prostate	—	77 mc.

Other random cases: brain tumours, 3.5 and 8.8 mc. respectively; carcinoma of the stomach, 150 and 90 mc.; hypernephroma of the kidney with ascites, 150 mc.; endothelioma of right lung, 78 mc.

The field of radiation and dose rates in the area surrounding the patient are depicted in Fig. 3.

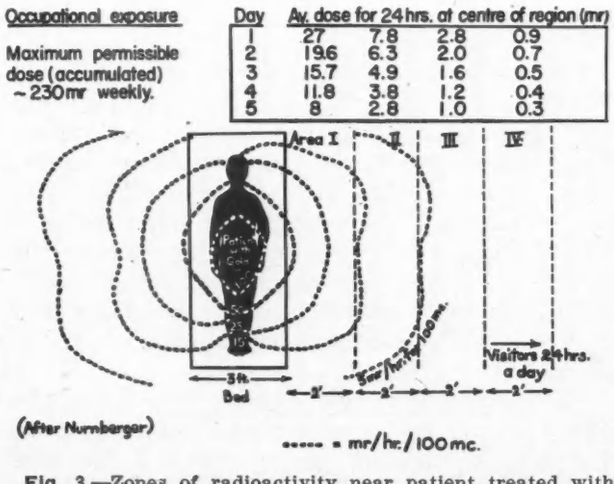

Fig. 3.—Zones of radioactivity near patient treated with gold. (See reference No. 5.)

TABLE I.—PATIENTS WITH MALIGNANCY AND ASCITES TREATED BY Au^{198}

Case	Sex	Age	Site of Au^{198} injection	Au^{198} instilled in mc.	Improvement	Survival after gold	Dead
Carcinoma of ovary:							
1	F	40	Abdomen	180	Some	20 months	Yes
2	F	46	Abdomen	190	No	2 months	Yes
3	F	74	Abdomen	150	No	1 month	Yes
4	F	53	Abdomen	100	Good for 5 months	7 months	Yes
5	F	57	Abdomen	148	Good	1 month	Alive
6	F	44	Abdomen	135	Slight	3 months	Yes
7	F	48	Abdomen	145	No	8 months	Yes
8	F	58	Abdomen	No	No	1 month	Yes
9	F	81	Abdomen	150	Good	7 months	Yes
10	F	61	Abdomen	150	Excellent	39 months	Yes
11	F	77	Abdomen	150	No	10 days	Yes
12	F	56	Abdomen	140	No	3 months	Yes
13	F	54	Abdomen	158	Slight	5 months	Yes
14	F	26	Abdomen	154	No	3½ months	Yes
15	F	54	Abdomen	114	Moderate	10 months	Yes
16	F	50	Abdomen	125	Excellent	50 months	Yes
17	F	63	Right chest	75			
			Left chest	36	Good	8 months	Yes
18	F	72	Abdomen	80			
			Right chest	90			
			Left chest	80	No	76 hours	Yes
Carcinoma of breast:							
19	F	62	Right chest	75	No	1 month	Yes
20	F	68	Right chest	75	Good	19 months	Yes
21	F	39	Left chest	65	No	2 days	Yes
22	F	50	Right chest	80	No	4 months	Yes
23	F	40	Abdomen	117	No	1 month	Yes
24	F	63	Left chest	115	Good	5 months	Yes
25	F	55	Abdomen	145	Slight	2 months	Yes
26	F	42	Right chest	98	No	3 months	Yes
27	F	51	Right chest	77	No	9 months	Yes
28	F	52	Abdomen	130	Moderate	8 months	Yes
29	F	54	Left chest	50	Slight	11 months	Yes
30	F	59	Abdomen	112	Good for 4 months	6 months	Yes
31	F	72	Left chest	90	No	3 weeks	Yes
32	F	48	Left chest	40	Good	30 months	Yes
33	F	56	Left chest	85	No	2 months	Yes
34	F	71	Right chest	75	Slight	8 months	Yes
Carcinoma of bronchus:							
35	M	25	Right chest	75	No	1 month	Yes
36	M	69	Left chest	80	Slight	1 month	Yes
37	F	38	Right chest	80	No	2 months	Yes
38	M	79	Right chest	50	No	3 months	Yes
39	F	67	Left chest	90	Moderate	22 months	Yes
40	F	60	Left chest	85	No	11 months	Yes
Carcinoma of stomach:							
41	M	69	Abdomen	90	Slight	5 months	Yes
42	M	50	Abdomen	150	No	1 month	Yes
Carcinoma of kidney:							
43	M	32	Abdomen	150	Moderate	3 months	Yes
Endothelioma:							
44	M	64	Right lung	78	Slight	16 months	Yes

RESULTS

The results in the 60 cases are summarized in Tables I, II and III. In general, no unusual symptoms were exhibited by the patients after instillation of the gold with the exception of one patient, Case 16 (carcinoma of the ovary with ascites), who was treated by 125 mc. Au^{198}. She had a period of nausea from which she quickly recovered. This patient had a most successful remission for a period of 50 months. Otherwise, there was only one other case of slight nausea and loss of appetite in the series.

The individual groups are not large enough to permit statistically significant conclusions, but from the point of view of general survival the most successful group is that of carcinoma of ovary without fluid, which is treated prophylactically with gold.

In those cases with fluid we have listed as improved those in whom the fluid diminished in quantity and the required number of paracenteses was reduced.

Amongst the treated patients with ascites, only 50% of those with carcinoma of the ovary and carcinoma of the breast showed any benefit and of these approximately half showed slight to moderate benefit and half showed good benefit.

A large group of those with carcinoma of the bronchus failed to show a response (67%) and the remainder of the group showed slight to moderate benefit.

TABLE II.—PATIENTS WITH MALIGNANCY AND NO ASCITES TREATED BY Au^{198}

Carcinoma of ovary (without ascites):							
45	F	47	Abdomen	118	Excellent	16 months	Alive
46	F	43	Abdomen	140	Good	18 months	Yes
47	F	45	Abdomen	114	Good	18 months	Alive
48	F	44	Abdomen	150	Excellent	5 months	Alive
49	F	68	Abdomen	105	Excellent	21 months	Alive
50	F	42	Abdomen	150	Excellent	2 months	Alive
Prostatic carcinoma:							
51	M	65	Prostate	78	Good	45 months	Yes
52	M	55	Prostate	100	No	15 months	Yes
53	M	63	Prostate	90	Moderate	11 months	Yes
54	M	73	Prostate	75	Good	66 months	Alive
55	M	74	Prostate	84	No	4 months	Yes
56	M	70	Prostate	40	Good	51 months	Yes
57	M	74	Prostate	75	No	2 months	Yes
Carcinoma of the breast (metastatic):							
58	F	69	Cystic brain tumour	3.5	Moderate	10 months	Yes
Craniopharyngioma (benign):							
59	M	25	Pituitary tumour	8.8	Good	45 months	Alive
60	M	29	Pituitary tumour	2.2	Good	1 month	Alive

In neither of the cases of cancer of the stomach with ascites was there any significant change after treatment; the patient with endothelioma and pleural effusion was only slightly benefited and the patient with carcinoma of the kidney with ascites was moderately benefited.

Our results do not appear as good as those of the 1899 cases compiled by Dybicki, Balchum and Meneely in 1959.[2] We do feel, however, that the use of radioactive gold is a worthwhile procedure.

In the main groups the average doses used were 70 and 77 mc. for intrapleural injection and 126 and 139 mc. for intraperitoneal injection. The average dose for prostatic carcinoma was 77 mc. of Au^{198}.

Good distribution of radioactivity without complications was achieved. There was one case of nausea, presumably associated with treatment.

Of those with carcinoma of the ovary with ascites 25% showed good results. Of those with carcinoma of the ovary without ascites 100% showed good results.

TABLE III.—SUMMARY OF RESULTS

Group	*Deceased*	*Alive*	*No benefit*	*Slight to moderate benefit*	*Benefit good*	*Average survival (months)*
Cancer of ovary (with ascites)	17	1	8	4	6	9.4
Cancer of breast	16	—	8	4	4	7
Cancer of bronchus	6	—	4	2	—	6.6
Cancer of ovary (prophylactic)	1	5	—	—	6	13.3
Cancer of prostate	6	1	3	1	3	21.3
Others (with ascites)	4	—	1	3	—	6.3
Others (without ascites)	1	2	—	1	2	18.7

Of the patients without ascitic fluid, the results were good in 100% of the group with carcinoma of the ovary (prophylactic use). Whether or not the gold was the main factor here is debatable.

In the prostatic carcinoma group, 43% showed no benefit, 14% slight to moderate benefit and 43% good results. In general the patients who had the best local response survived the longest.

In the three miscellaneous cases treated, moderate to good results were obtained.

None of those with carcinoma of the bronchus responded well. Of patients with carcinoma of the prostate 43% showed some improvement. Of the miscellaneous cases, Cases 41-44 (Table II) did unusually poorly. The remaining cases, Cases 58-60 (Table II), did fairly well.

SUMMARY

Sixty patients were treated by means of instillation of Au^{198} in an attempt to reduce or stop fluid production, diminish tumour size or prevent metastatic spread of spilled malignant cells. Forty-four patients had malignant effusions, six were treated prophylactically, seven had prostatic carcinoma and three had cystic brain tumours.

All were proven malignant (except Cases 59 and 60).

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SIMPLIFIED TECHNIQUE FOR EXAMINATION OF CHROMOSOMES IN THE BONE MARROW OF MAN

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THE SOMATIC chromosome number of man was generally considered to be $2n = 48$ until Tjio and Levan[13] and Ford and Hamerton[6] published their observations indicating that the true somatic number was 46. This chromosome number was confirmed by Ford, Jacobs and Lajtha[7] and by many others. With recent advances of techniques, chromosomes have been the subject of detailed morphological analysis. The method described by Ford, Jacobs and Lajtha[7] is in general use with some minor modifications. The basic steps in this technique are the short-term culture of bone marrow cells in the presence of colchicine, the treatment of the cells with a hypotonic solution, staining with Feulgen and subsequent squashing under a coverglass. Colchicine inhibits spindle formation, causes accumulation of metaphases and shortens the chromosomes, thus facilitating their examination. Hypotonic solutions cause cellular swelling and disperse the chromosomes throughout the mitotic cell.

It is in the field of development of tissue and cell culture techniques that the greatest advantages for cytological studies are claimed. The growth zone often consists of a single layer of cells, thus facilitating experimental treatments, cytological fixation and staining. Mitotic activity usually is more enhanced *in vitro* than *in vivo*, and it can be subjected to experimental control. The cells tend to be flattened and stretched on the substrate.[3]

The use of cell culture techniques can be criticized because of karyotypic changes which may occur during growth *in vitro*, although in short-term cultures this problem is unimportant. The cells in tissue culture may fail to divide. As a general rule, direct examination of cells, when possible, is to be preferred to examination of those obtained from tissue culture. Another valid criticism of cell culture is that it is a specialized technique. Study of chromosomes therefore has been confined to centres where tissue culture facilities are available.

The object of this communication is to describe a simple technique which does not require tissue culture for examination of the chromosomes in man. Deacetylmethyl-colchicine (Colcemide) is administered to the subject before bone marrow aspiration. This avoids the necessity of tissue culture.

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MATERIAL

Bone marrow was obtained from 23 patients with cancer and allied disorders and from eight mental hospital patients suffering from various congenital diseases. The posterior ilium was preferred to the sternum as a site of bone marrow aspiration because of the complete freedom from risk and the lessened psychological disturbance to the patient.

METHODS

The methods involve treatment of the patient and of the specimen of bone marrow obtained. These will be considered separately.

The patient is given an intravenous injection of deacetylmethyl-colchicine (Colcemide) in a dose of between 0.05 and 0.1 mg. per kg. of body weight. A specimen of bone marrow is obtained by aspiration 3 to 24 hours later.

The specimen of bone marrow is placed in a solution of 0.5% sodium citrate and agitated gently. After centrifugation, the supernatant fluid is discarded and the cells are re-suspended in 0.5% sodium citrate and incubated at 37° C. for 15 to 30 minutes. The specimen is again centrifuged and the supernatant fluid is discarded; 45% acetic acid is then added and the cell "button" is dispersed with a needle or fine rod. The specimen should remain in acetic acid for at least 20 minutes. At this stage, the specimen can safely be stored in a refrigerator if examination cannot be performed conveniently. After recentrifugation the supernatant fluid is again discarded and a few drops of filtered 2% aceto-orcein stain are added. The cell "button" is dispersed with a needle or fine rod. The optimum amount of stain to be added depends upon the cellularity of the bone marrow aspirate and is learned by "trial and error"; it is to be remembered that while more stain can be added, none can be withdrawn. Staining should continue for 20 minutes. A drop of the preparation is placed upon a glass slide and a coverglass is placed upon it. Heavy but even pressure is applied to the coverglass after excess of stain has been absorbed by a paper towel. If any lateral movement of the coverglass should occur during "squashing", the slide should be discarded. The coverglass is sealed with paraffin. Several preparations should be made.

Examination is carried out under phase contrast microscopy. The slide is first examined under low-power magnification and cells suitable for chromosome study are selected. Chromosomes can only be examined adequately under the oil immersion lens. Cells are selected in which the chromosomes are well spread and lie, as far as possible, in the same optical plane. Chromosome enumeration or morphological study should not be performed on cells which are ruptured.

DISCUSSION

Several technical difficulties were encountered with this method. It was found impossible to pre-

dict which specimen of bone marrow would give a high yield of cells suitable for chromosome examination. There are several reasons for this. The amount of dilution with peripheral blood is variable; an active or a hyperactive bone marrow will contain many cells in mitosis, while a relatively hypoactive bone marrow will not. Considerable variation in chromosome spreading is encountered in different slides even when they have been prepared from the same cellular suspension. This variation from one slide to another probably represents the result of minor differences in "squashing" techniques, such as those resulting from slight lateral movement of the coverglass or variation in the amount of pressure used. Differences in room temperature and in cellular sampling may also contribute in this regard.

The time interval between the injection of the Colcemide and the aspiration of the bone marrow varied between 1½ and 72 hours. Specimens obtained less than three hours after Colcemide injection were usually unsatisfactory, showing lack of chromosome shortening and poor dispersal. Specimens obtained up to 24 hours after the Colcemide injection gave satisfactory results. Those obtained more than 24 hours after the Colcemide injection showed a higher proportion of telophases. This was interpreted as indicating the end of the colchicine effect.

Several concentrations of sodium citrate solution were tested. While 0.5% gave the most consistent results, there were a few occasions when a 1% solution gave superior preparations.

It will be appreciated that with all these variable factors, an extremely large series of cases would be necessary to establish the optimum technical conditions. The method here described is compended from the experience obtained from 30 specimens.

With regard to the examination of the chromosomes it is of assistance to draw or take a photomicrograph of the cell and then enumerate and identify the structures in conjunction with the pictorial representation. Centromere position and relative length are the principal features used for the identification of the individual chromosomes.

In May 1960, at the suggestion of Dr. C. E. Ford, a group of cytologists met at Denver and formulated a common system of chromosome nomenclature. Their proposed standard system was published in several medical journals, including the *Lancet* and the *Canadian Medical Association Journal* (1960). For information about the interpretation of chromosome counts made on bone marrow cells, reference should be made to the contribution by Court Brown, Jacobs and Doll.[4] A description of the various conditions in which chromosomal abnormalities have been discovered is not within the scope of this communication.

Colchicum was introduced for the therapy of acute gout by Baron Anton von Storck in 1763 and remains in widespread clinical use. The action of colchicine is a direct one upon cell division which results in an arrest of mitosis in the metaphase due to interference with spindle formation.[8] Deacetylmethyl-colchicine (Colcemide) has an antimitotic activity similar to that of colchicine, but its toxicity is 30 times less.[12] In man, Colcemide has been used in the treatment of chronic myelogenous leukemia[10] and in patients with carcinoma and sarcoma.[12] In oral dosage of 3 to 7 mg. daily, no significant toxic effects were observed. Bock and Gross[1] gave up to 16 mg. daily by intravenous injection without encountering significant toxic effects. No toxic effects were observed in our group of patients. Bottura and Ferrari[2] describing a similar technique noted no toxic effects after the injection of Colcemide in a dose of 0.1 mg. per kg. of body weight in a group of eight patients. It would seem that, in the absence of actual marrow hypoplasia, there is no immediate danger in the administration of a single injection of Colcemide in a dose of 0.05-0.1 mg. per kg. of body weight.

On the other hand, any drug, such as Colcemide, which possesses such a fundamental effect upon the nuclear constituents of the dividing cell, must come under suspicion with regard to the production of mutations. D'Amato and Gustafsson[5] analyzed the combined influence of x-rays and various chemicals on the mutation process, in barley seeds. They found that pretreatment with several substances increased the rate of mutation. Colchicine in low concentrations did not significantly increase the mutation rates, but it distinctly widened the range of mutability. Colchicine also induced some previously unknown mutations.

Scant information is available about the production of mutations with Colcemide in man. Colchicine has been used for many years in the treatment of gout without being incriminated in this respect, but such patients are very often past the reproductive age. Cases have been reported[11, 14] where conception and delivery of normal children have occurred while the patient was receiving treatment with Colcemide for chronic myelogenous leukemia.

Whether or not Colcemide, in a single dose, can induce mutations in man should be regarded as undecided. For this reason Colcemide should not be administered indiscriminately. In the present series, the patients were beyond the age of childbearing, had had endocrine ablative procedures which would render reproduction impossible, or had such a poor prognosis that the risk of producing mutations was negligible.

It has been stressed by several observers that Colcemide should not be used in the treatment of lymphatic leukemia as it may cause an acute exacerbation.

SUMMARY

A simplified method for the examination of the chromosomes in the bone marrow in man is described. It involves the pretreatment of the patient with deacetylmethyl-colchicine (Colcemide) by intravenous in-

jection in a dose of 0.05-0.1 mg. per kg. of body weight. The specimen of bone marrow is then exposed to the effects of a hypotonic solution of sodium citrate and a strong solution of acetic acid, and is stained with aceto-orcein. The methods of examination are described briefly.

The risk of inducing mutations with Colcemide is discussed and it is stressed that the drug should not be administered indiscriminately.

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SPECIAL ARTICLE

SMOKING HABITS OF WINNIPEG SCHOOL CHILDREN*

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LUNG CANCER has increased at an alarming rate, greater than any other major disease. Table I illustrates the increase in the male death rate over an eight-year period in Canada[10] and compares it with that for all other forms of cancer. This represents a 48% increase in male lung cancer compared with a slight decrease in the total deaths from all other forms of cancer. In 1960 Winnipeg[8] had 80 deaths from lung cancer. There were 43 deaths from traffic accidents, 12 from tuberculosis in the same year and 35 deaths from poliomyelitis in 1953 when Winnipeg suffered one of the most severe poliomyelitis epidemics recorded in any North American city.

In 1958 vital statistics reports[10] for Canada, the latest available, there are 2263 deaths from primary lung cancer, and 1845 from all infectious diseases including tuberculosis. The figures for males alone are even more striking: 1972 lung cancer deaths to 1149 from all infectious diseases. In males the lung is now the most common site of primary cancer.

Even with present case-finding methods, surgery and other treatment, lung cancer still has a case fatality rate of more than 95%. It is, therefore, essential that serious consideration should be given to methods of prevention.

The Medical Research Council of Great Britain,[14] the Surgeon General of the United States Public Health Service[3] and the American Cancer Society[16] have all stated that there is sufficient evidence to establish a causal relationship between cigarette smoking and lung cancer. They and others[4, 5, 12] have, therefore, advised the launching of educational campaigns to reduce smoking. In view of this, the City of Winnipeg Health Department in conjunction with the School Board decided to investigate present methods of education about smoking. As an initial step we decided to survey the present smoking habits of Winnipeg School Children from grade five to grade twelve, inclusive. We felt that this would give us information about the pattern of cigarette smoking in Winnipeg school children, the age at which smoking first started and a baseline standard with which to compare the results of any educational program.

MATERIALS AND METHODS

The population surveyed consisted of an estimated 25,103 students in grades five to twelve inclusive. The survey was carried out in May 1960, and consisted of submitting a questionnaire to the school children. This questionnaire was similar to that used by the London School of Hygiene.[13]

The authors explained the questionnaire and its purpose to the principals of the schools, who in turn interpreted it to the teachers who administered the questionnaire in the classrooms. The questionnaires were answered anonymously. Replies were made by circling the appropriate answer and the students were informed that they could leave out any questions they wished. This was to avoid any charges of prying into the private lives of the children and their parents. The completed questionnaires from each classroom were placed in an envelope and the academic grouping of the class (e.g. Average, Above Average, Major Work, etc.) was marked on the envelope by the principal or teacher. The data from each questionnaire (as shown) were placed on an IBM punch card.

A repeat survey in a 2% sample of classrooms selected to give the same distribution of sex and grades as the total survey was carried out with the

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WINNIPEG HEALTH DEPARTMENT

QUESTIONNAIRE ON CIGARETTE SMOKING HABITS

School Number: Room Number:

MAKE A RING AROUND YOUR ANSWER TO EACH OF THE QUESTIONS

1. I am.....	A BOY A GIRL
2. My age is.....	8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, over 20
3. At what age did you smoke your first cigarette?.....	6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, Never
4. Does you father smoke?..	YES NO
5. Does your mother smoke?	YES NO
6. Have you smoked in the LAST FOUR WEEKS?..	YES NO

If the answer to question 6 is YES, answer questions 7 and 8.
If not, DO NOT answer questions 7 and 8.

7. How many cigarettes do you usually smoke in a week?.....	(1) Less than 1 (2) 1—4 (3) 5—9 (4) 10—19 (5) 20—39 (6) 40 or more
8. At what age did you start smoking ONE OR MORE CIGARETTES A WEEK?	6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20

authors administering the questionnaire. This was done as a check on the validity of the answers in the original survey. As it was impossible to complete this repeat survey before the end of the term, it was done in the fall, and the comparison made with equivalent rather than identical classes.

In order to allow for considerable age and sex variation in the different academic groups we calculated "Comparative Smoking Indices" similar to the "Comparative Mortality Indices" used in studies on mortality rates of specific groups to rule out effects of different age and sex distribution. The proportion of smokers for each age group in the two sexes was calculated for all students irrespective of academic grouping. The figures obtained were then applied to the academic groups separately to give an "expected" number of smokers on the hypothesis that the variation of the number of smokers in each group was attributable solely to the variation in age composition. The "observed" number of smokers as obtained from the results of the questionnaire was then compared with the "expected" number of smokers. The comparative smoking index was obtained by dividing the observed number of smokers by those expected.

That is:

$$\text{Comparative Smoking Index} = \frac{\text{Observed Smokers.}}{\text{Expected Smokers.}}$$

Unity indicates that the proportion smoking in that group was the same as for all students combined, i.e. it represented an average smoking rate. Values greater than unity indicate a smoking rate greater than average; values below unity, less than average.

The large number used in this survey gave figures which were highly significant on the chi-square test. Conclusions are based on this test.

RESULTS

A total of 22,386 questionnaires were returned and of these 502 were rejected. Twelve from a special class for partially sighted children and 20 from a class of new immigrants learning English were rejected, as these two groups could not be classified into grade and academic achievement. The other 470 were rejected because of incompleteness. Twenty-five had not stated a sex, and 36 did not state an age; 100 gave sex and age, and answered questions on their parents' smoking habits, but did not answer any questions about their own smoking habits and were possibly non-smokers. In all 21,884, or 97.7%, of the questionnaires were used, representing returns from 87.2% of the student population studied. Returns diminished with the higher grades: grades five and six, 91.5%; seven to nine, 89.8%; and ten to twelve, 83.8%. Throughout this report all references to smokers means smoking one or more cigarettes a week unless otherwise stated. This is the criterion used by Horn *et al.* of the American Cancer Society.[12]

Fig. 1 and Table II show the general smoking pattern. The grades are grouped according to the pattern in the Winnipeg schools. Grades five and six are the final years of the "elementary schools" and the typical age in these grades would be 11 and 12 in May at the end of the school year. Grades seven, eight and nine are grouped as "junior high" in this city, and typical ages would be 13 to 15 years of age. The grades ten, eleven and twelve make up the "high school" classes. Generally the elementary, junior high, and high schools are

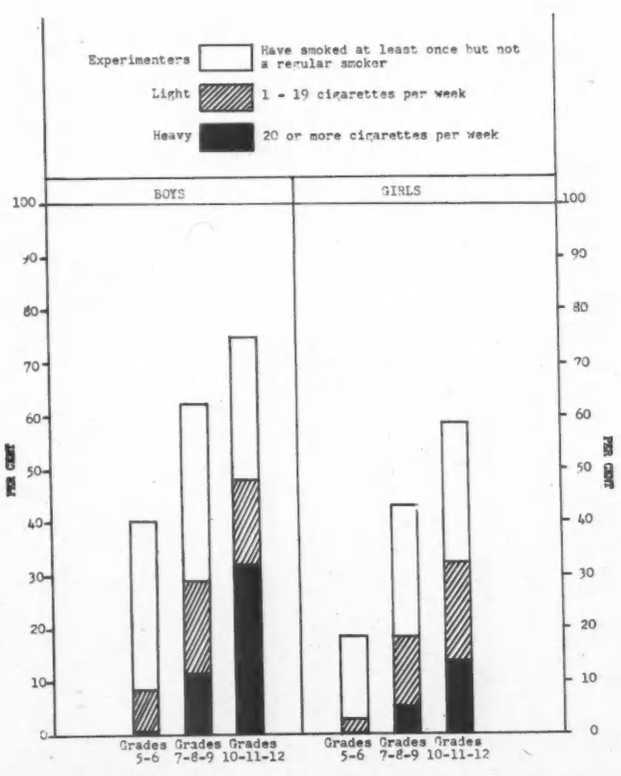

Fig. 1.—Smoking habits of Winnipeg school children. A study of 21,884 Winnipeg school students grades 5-12 inclusive, May 1960.

TABLE I.—A COMPARISON OF MALE DEATHS FROM CANCER OF LUNG WITH MALE DEATHS FROM ALL OTHER FORMS OF CANCER, CANADA 1951 - 1958

Year	*Cancer* of lung*	*Rate per 100,000 population*	*All other† cancer*	*Rate per 100,000 population*
1951	1095	15.4	8314	117.3
1952	1251	17.1	8874	121.6
1953	1383	18.5	8941	119.6
1954	1498	19.5	9211	119.9
1955	1621	20.6	9564	121.3
1956	1775	21.8	9749	119.6
1957	1849	22.0	9891	117.5
1958	1972	22.8	9994	115.6

*International Intermediate List No. A50.
†All neoplasms except A50.

separate institutions, although there are some combined junior and senior high schools. There are also 97 boys and 78 girls listed as "ungraded"; these students are in special ungraded classes for children of low I.Q. and their age and grading cannot be fitted into the other groups.

a shift to heavier smoking with increasing grades (Table II), and Table IV shows these figures by age for boys alone. This indicates that the median figure for the amount of smoking lies in the 1-4 cigarettes per week range for boys under 14 years of age. It then increases to 40 or more per week by 17 years of age.

The relationship between parental smoking habits and those of the children is shown in Table V and Fig. 3. Even where neither parent smokes, 20.8% of the boys had smoked in the last four weeks. This proportion was increased by about 38% when either or both parents smoked, but there was no real difference in boys' habits with the different positive smoking habits of the parents.

Fewer girls smoke when neither parent smokes than when parents smoke, and the girl is much more closely tied to her mother's smoking habits. Her smoking is increased by 33% when the father

TABLE II.—SMOKING HABITS OF WINNIPEG SCHOOL CHILDREN. A STUDY OF 21,884 WINNIPEG SCHOOL STUDENTS GRADES 5 - 12 INCLUSIVE, MAY 1960

	Boys				*Girls*			
	Grades 5 - 6	*Grades 7 - 8 - 9*	*Grades 10 - 11 - 12*	*Ungraded*	*Grades 5 - 6*	*Grades 7 - 8 - 9*	*Grades 10 - 11 - 12*	*Ungraded*
Number in group	3544	4897	2737	97	3497	4702	2332	78
Never smoked	59.5%	37.6%	25.2%	29.9%	81.3%	56.9%	41.4%	57.7%
Had smoked, but not in last 4 weeks	31.8%	33.1%	26.8%	35.1%	15.6%	24.5%	26.2%	7.7%
Number smoked per week in last 4 weeks by those who smoked:								
Less than 1	2.9%	3.9%	3.3%	7.2%	1.1%	3.1%	4.2%	3.8%
1 - 4 per week	3.4%	5.6%	4.0%	12.4%	1.3%	4.3%	5.3%	9.0%
5 - 9	1.0%	3.6%	3.2%	1.0%	0.4%	2.9%	4.0%	7.7%
10 - 19	0.7%	4.6%	5.3%	5.1%	0.1%	2.9%	4.9%	7.7%
20 - 39	0.5%	5.1%	8.8%	6.2%	0.1%	2.9%	5.7%	5.1%
40 or more	0.2%	6.5%	23.4%	3.1%	0.1%	2.5%	8.3%	1.3%
Total (one or more per week)	5.8%	25.4%	44.7%	27.8%	2.0%	15.5%	28.2%	30.8%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

In Fig. 1 the bars indicate the per cent of students in each group who have smoked. The space between the top of the bar and the top of the chart, therefore, indicates the proportion of students who have never smoked. Students who have smoked but were not smoking at the time of the survey are listed as "experimenters" on the chart. Those smoking regularly were arbitrarily subdivided into "light" smokers if smoking 1-19 cigarettes a week, and "heavy" smokers if smoking 20 cigarettes or more a week.

Boys smoke more than girls in all grades. In elementary grades regular smoking was very light although present, but about 40% of the boys and 18% of the girls have smoked their first cigarette. In junior high school, smoking is not at all uncommon, 25.4% of the boys and 15.5% of the girls smoking regularly. In high school 44.7% of the boys and 28.2% of the girls stated that they smoked regularly.

Table III shows this increase by age and sex rather than by grade. It is seen that the greatest increase occurs between 13 and 16 years of age (the junior high school age group). There is also

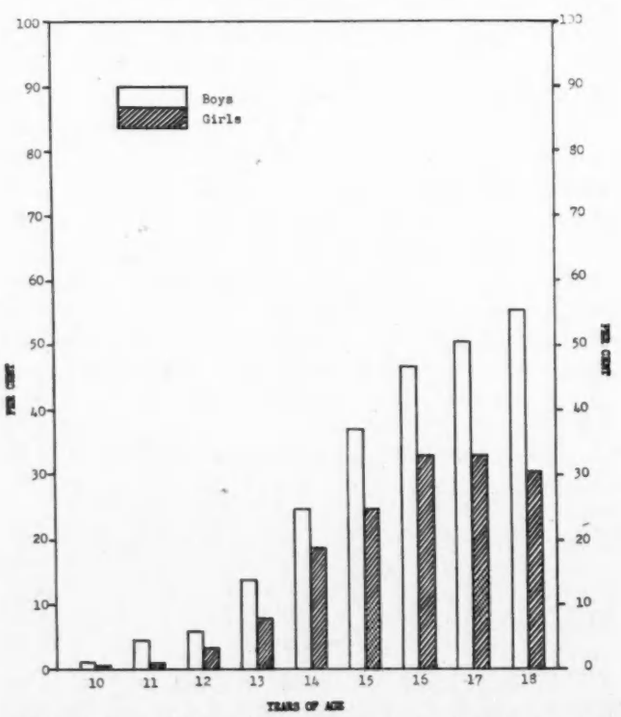

Fig. 2.—Per cent of students who smoke more than one cigarette a week by age and sex.

TABLE III.—SURVEY OF SMOKING HABITS OF 21,884 WINNIPEG SCHOOL CHILDREN, MAY 1960

(a) Students who smoke more than one cigarette a week by age and sex.
(b) Ratio of girls to boys in the school population by age.

	BOYS			*GIRLS*			
		Smoked more than one a week			*Smoked more than one a week*		
Age (1)	*Total* (2)	*Number* (3)	*%* (4)	*Total* (5)	*Number* (6)	*%* (7)	*Ratio of girls to boys* (8)
9	29	1	3.44	57	—	—	1.96
10	731	8	1.09	803	3	.37	1.10
11	1394	60	4.30	1485	14	.94	1.07
12	1622	95	5.86	1731	55	3.17	1.07
13	1893	259	13.68	1725	135	7.82	.91
14	1387	339	24.44	1406	260	18.49	1.01
15	1319	486	36.84	1218	299	24.55	.92
16	1243	582	46.82	1193	393	32.94	.96
17	971	487	50.15	766	252	32.90	.79
18	480	265	55.21	181	55	30.39	.38
19	155	87	56.13	39	9	23.08	.25
20	25	13	52.00	2	—	—	.08
20 plus	26	21	80.77	3	2	66.67	.12
TOTAL	11,275	2703	23.97	10,609	1477	13.92	.94

is the lone smoker, but by 76% when the mother or both parents smoke.

Information on the smoking habits of the parents as given by the students is shown in Table VI. There was no statistical difference between the answers of boy and girl students. Only 18.41% of the students have no parent smoking. There was no question asked as to smoking amongst other household adults, such as older siblings and relatives, so that absence of smoking at home probably occurs in even less than 18% of families. The most common pattern was for both parents to smoke, and next for the father alone to smoke. In less than 9% of the homes the mother was the only parent smoking. The combined figures indicate that almost 73% of the adult male parents and 50% of the mothers smoke.

Smoking habits of students have an inverse

TABLE IV.—BOYS BY AGE WHO HAVE SMOKED IN THE LAST FOUR WEEKS

	Number of cigarettes smoked per week						
Age	*Less than one*	*1 - 4*	*5 - 9*	*10 - 19*	*20 - 39*	*40 or more*	*Total*
9	1*					1	2
10	13*	6	2				21
11	45	47*	6	2	4	1	105
12	46	55*	20	10	6	4	141
13	82	114*	58	34	33	20	341
14	69	92	63*	75	59	50	408
15	54	86	52	105*	115	128	540
16	40	60	58	81	137*	246	622
17	30	31	31	52	105	268*	517
18	5	16	10	28	35	176*	270
19	4	9	3	9	17	49*	91
20		2		1	1	9*	13
20 plus	1		1	1	2	17*	22
	390	518	304	398	514	969	3093

*Indicates column in which the median figure for number of cigarettes at each age will fall.

TABLE V.—RELATIONSHIP BETWEEN SMOKING HABITS OF STUDENTS AND THOSE OF THEIR PARENTS

A STUDY OF 21,527 WINNIPEG SCHOOL STUDENTS, GRADES 5 - 12 INCLUSIVE, MAY 1960

	Boys				*Girls*			
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
	Father smokes	*Mother smokes*	*Both parents smoke*	*Neither parent smokes*	*Father smokes*	*Mother smokes*	*Both parents smoke*	*Neither parent smokes*
Number of students	3536	994	4518	2055	3241	876	4398	1909
Never smoked	40.1%	39.6%	41.1%	45.4%	63.5%	57.8%	58.2%	69.0%
Smoked, but not in last 4 weeks	31.9%	31.6%	29.5%	33.8%	21.7%	22.5%	22.2%	19.9%
Smoked in last 4 weeks	28.0%	28.8%	29.4%	20.8%	14.8%	19.7%	19.6%	11.1%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

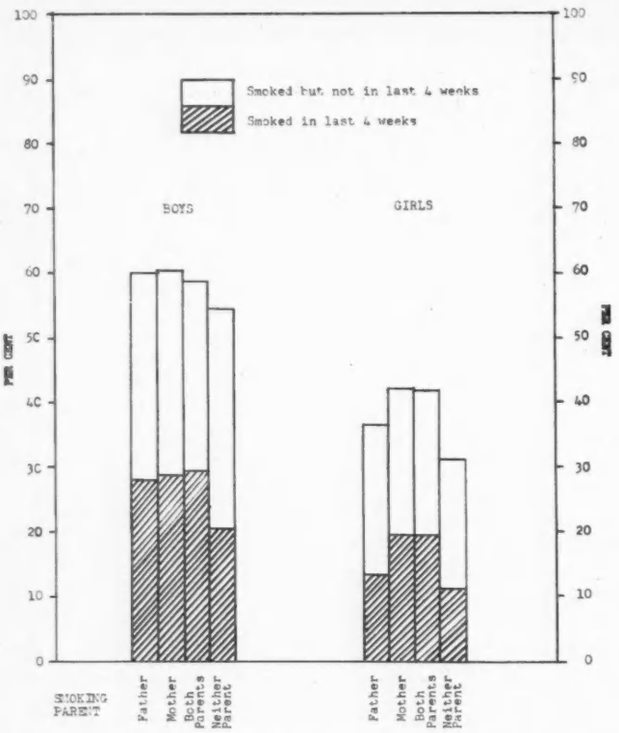

Fig. 3.—Relationship between smoking habits of students and those of their parents.

TABLE VI.—SMOKING HABITS OF PARENTS OF 21,527 STUDENTS (357 students did not answer this question)

Smokes	*Number*	*%*
1. Father alone	6777	31.48
2. Mother alone	1870	8.68
3. Both parents	8916	41.41
4. Neither parent	3964	18.41
TOTAL	21,527	100.00
5. Father (1 + 3)	15,693	72.89
6. Mother (2 + 3)	10,786	50.10

relationship with academic achievement (Table VII). This inverse relationship is shown more strongly in girls. The ungraded classes do not conform to this pattern in either sex but the numbers are very small.

The repeat survey done in September 1960 was tabulated only as in Table II, and compared with a similar tabulation of equivalent classes from the same schools in the original survey. The patterns were quite similar throughout and there was no statistical difference in the results.

Students were asked "At what age did you smoke your first cigarette?" Tabulation of the answers to this question is complex, as the age at which the question was asked must be taken into account. However, 565 stated that they had smoked by six years of age, and an additional 975 by eight years of age.

DISCUSSION

1. *Conduct of Survey*

The announcement of the proposed survey was met by editorial criticism in both Winnipeg daily newspapers. The chief criticism was that we were prying into the private lives of the parents through their children in the questions on parental smoking habits. It was also suggested that such a survey might lead to further surveys with more detailed and intimate questions. The questionnaire from the start was to be answered anonymously. In order to avoid the criticism of prying, students were told that they could leave out answers to questions to which they objected. However, the number of unanswered questions was negligible, 98.4% answering the most contentious question, that on parental smoking. No criticism of the survey was received by the Health Department from parents, and several commendations of the project were received from parents and interested persons. The second "fear" was fulfilled in the fall of 1960 when the Alcohol Education Committee requested permission to conduct a survey in the schools. Their request was refused by the elected School Board.

2. *Validity of Results*

The questions were kept to a minimum, only eight being asked. They were simple questions, which could be answered by circling the correct answer. Most of the questions were about present habits which the student would be expected to

TABLE VII.—COMPARATIVE SMOKING INDEX BY ACADEMIC STANDARD AND SEX OF 21,884 WINNIPEG SCHOOL STUDENTS GRADES 5 - 12 INCLUSIVE, MAY 1960

	Boys				*Girls*			
Type of class	*Total number*	*Smokers*	*Expected No. of smokers*	*C.S.I.**	*Total Number*	*Smokers*	*Expected No. of smokers*	*C.S.I.**
Honours	183	26	77	0.34	175	17	51	0.33
Major work	410	23	47	0.50	344	11	28	0.39
Above average	2011	224	362	0.62	2342	150	265	0.57
Average	5780	1403	1407	1.00	5518	812	811	1.00
Below average	2528	867	696	1.25	1955	376	276	1.36
Slow learners	266	129	86	1.50	197	85	43	1.96
Ungraded	97	31	30	1.04	78	26	16	1.59

*Comparative smoking index.

Comparative smoking index is obtained by applying the observed number of smokers to the expected number of smokers.

The expected number of smokers is calculated by applying the age and sex specific smoking rates of the entire tested school population to the age and sex specific population in the specific subgroup under study.

know without having to recollect. There was one question with reference to the age at which the student first smoked, and a second which asked at what age he began to smoke regularly. There was no provision for the answer "don't know" concerning parental smoking, or "separated from parent". We realize now that this should have been included. A frequent query from the students was "What shall I put if my parent used to smoke, but quit?" These students were advised to answer that their parent did not smoke.

With the exception of these questions, therefore, we feel that the student would have no trouble knowing and giving the correct answer. The anonymity of the answers was stressed to assure confidential replies. It might be expected that some of the students would take the survey lightly, but only one questionnaire had obviously "smart alec" replies. It had been hoped that the repeat survey, which was very carefully carried out by the two authors, would be done within the same school term so that the comparisons would be with the same students. In this case almost identical results would have been expected if original and second answers had both been accurate. Owing to unexpected delays in getting the survey under way, the repeat survey could not be done in the same term, and the comparison with equivalent classes gave no indication that previous results were out of order. A breakdown of the results into different districts showed similar patterns in each district studied. A Norwegian[15] study was followed by a sample personal interview study and it was found that, if anything, personal interviews yielded a higher percentage of positive answers as to smoking history.

3. *Development of Smoking*

The increase in smoking in the 13-16 age group is similar to findings in other surveys.[2, 7, 9, 11-13, 15] It is difficult to make quantitative comparisons with other surveys because of the differences in the school systems and slightly different criteria in the definitions of "smoking". A publication of the American Cancer Society[1] quotes a report that 16% of 13-year-olds smoke and 52% of 18-year-olds. Our figures for these ages in males are 13.68% and 55.21% respectively.

The study of smoking habits of the University of British Columbia[9] students is the only one which we have noted that does not show a lighter smoking pattern among females than males, but their study was a select group. The European studies seem to show a lighter smoking pattern in both sexes but this is difficult to assess. However, they do seem to show this much more markedly in girls, i.e. European girls smoke less in proportion to boys than in North America.

The levelling off of the percentage of girls who smoke after 16 years of age probably can be explained by a change in the make-up of the female school population at this age level. In Manitoba there is compulsory school attendance to the age of 16. As indicated in column 8 of Table III, girls drop out of school much more rapidly after 16 than do boys. A study of the school census shows that the decrease in girls at school occurs mostly in the lower academic groups where the Comparative Smoking Index indicates that the smoking habit is strongest. It is probable that if these girls had not left school their influence on the survey would have been to show a continuing increase.

4. *Relationships of Smokers*

In addition to the questions on present smoking habits to illustrate the present pattern in the schools, attempts to elicit reasons for smoking were made by asking about parental smoking habits and by comparison of smoking in different academic classifications. Our findings with both these relationships are similar to other studies. The girls show a more marked influence by parental smoking habits, particularly of their mothers. They also show the decrease in smoking with higher academic standing, and vice versa, more markedly than do boys.

Our study does not indicate whether academic success affects smoking, or whether smoking affects academic success, but it is most likely that the former is the case. Others[6, 12] have shown that students who were successfully involved in extra-curricular sports and social activities also smoke less and that there is an association between non-smoking and industriousness, ambition, asceticism and religious observance.

It is difficult to say that the pattern of adult smoking among the parents is that for all adults. However, a British survey of adults showed that 74% of males and 37% of females were currently smoking.

The responses to retrospective questions as to smoking first cigarettes and onset of regular smoking are not as reliable as the responses to the other questions. A considerable number had smoked their first cigarette by six years of age and the following two years. Children at these ages, like everyone else, are subjected to cigarette advertising on television and radio and the influence of smoking at home, and it is quite reasonable to expect an interest in the subject at an early age, the more venturesome experimenting with smoking if the opportunity arises.

CONCLUSIONS

A considerable number of students have smoked their first cigarette as early as six years of age. Therefore, the subject of smoking is in the minds of some students from school entrance and some casual reference to the subject is in order throughout elementary school.

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An active program of smoking education should be carried out in the junior high schools. Particular stress is needed in the classes of lower academic standing, and among boys.

Smoking education starting after 16 years of age is probably too late in many cases. It will also miss those who drop out of school because of poor academic standing, and these appear to be the ones most in need of such education.

SUMMARY

Current medical thinking indicates that lung cancer, which accounts for a fifth of all male cancer, is a potentially preventable disease through reduction in smoking, particularly cigarette smoking.

As a preliminary step to the introduction of a more realistic health education program designed to curb the incidence of cigarette smoking, a survey of the smoking habits of 21,884 Winnipeg school children was completed in May 1960.

The survey indicated that some children began to smoke very early and that the greatest increase was in the 11-16 year age-group. Students are influenced by their parents' smoking habits, and smoking is inversely related to academic achievement.

Health education to prevent the adoption of the smoking habit must begin earlier than has been the practice and must be more closely related to present scientific knowledge. It must involve the youngest children in a casual way. Emphasis must be directed to the early teenage student.

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MEN AND BOOKS

NO LONGER CAPTAIN: A HISTORY OF TUBERCULOSIS AND ITS CONTROL AMONGST CANADIAN INDIANS

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FOR DECADES the tubercle bacillus, as "captain of the hosts of death", marched its forces against the Indians of this country, taking lungs instead of scalps. This paper tells of some of the factors that have forced this grim captain from its position as the leading killer of our native population until today it lurks in the shadows, ranking only eighth. In 1959 the Indian death rate from tuberculosis was lower than that for all of Canada at the end of World War II.

The history of this disease among the Indians, and the epidemic and pandemic proportions it reached, poses many questions and presents large fields for speculation.

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There is some evidence, according to anthropologists, that tuberculosis was present in North America before the arrival of the white man. It has been stated that examination of skeletons predating the arrival of Europeans, notably in so-called Huronia and among the ancient cliff dwellers, revealed tuberculous lesions of the bones.

Why did the Indians of eastern Canada, who were the earliest contacts of the white man, never seem to develop tuberculosis to the epidemic proportions it reached among the western Indians, particularly those of the Great Plains? This is particularly surprising, since tuberculosis was rife among the early French and English settlers. As late as 1830 the tuberculosis death rate for Boston, New York and Philadelphia combined was 465 per 100,000.

Dr. Robert George Ferguson, known to the Crees of the Qu'Appelle Valley as "Muskeeke-O-Kemamam" (the Great White Physician), has recorded the ravages of this disease in his article "Tuberculosis Among the Indians of the Great Canadian Plains".[1] Much of the following material is quoted

directly from this paper and from his book, "Studies in Tuberculosis".[2]

Dr. Ferguson states:

"A study of the Indians in the Qu'Appelle Valley area in Saskatchewan from the time treaty money was first paid in 1874 up to 1926, a period of fifty years, has shown that the health record was predominantly the history of an acute epidemic of tuberculosis.

"A survey of available sources of information indicates that among the Plains Indians of Western Canada, even in their natural state as buffalo hunters, sporadic cases of tuberculosis spread steadily in the interval up to 1880. However, tuberculosis was not then a scourge among the Indians, and it was not the major cause of death until after they had settled on the reserves in the 1880's. . . .

"The obvious conditions facilitating the progress of the epidemic and the spread of infection at this time were the concentration of the Indians in fixed residences on the reserve, lack of sanitation, their contact with the surrounding white settlers, and the concentration of the children in boarding schools for education. Under these conditions tuberculosis infection spread quickly. . . .

"Vital statistics records for these reserves show that the tuberculosis death rate rose from approximately 1000 per 100,000 in 1881 to 9000 per 100,000 in the same five years.". . . Evidently the rise in the general death rate was due almost entirely to the increase in the tuberculosis death rate.

"In 1884, three years after the Indians had settled on the reserves, the Indian children were brought very closely together in dormitories in large boarding schools. This increase in contact assured the complete tuberculization of the second generation and a very high infection rate among the school children followed. Interval tuberculin tests made of children attending these schools during the years 1926 and 1928 confirmed the extent of the tuberculization. These tests indicated that under conditions obtaining in the Indian boarding schools where there were spreaders of tuberculosis, children with negative tuberculin reactions on entering school became positive reactors within two years. . . .

"In the acute stage of the Indian epidemic, phenomenal glandular involvement was observed by all physicians and others who had the opportunity of witnessing the epidemic. The common picture among these Indians was generalization of involvement of the lymph gland system, frequently described as scrofula. The cervical, axillary, and inguinal glands, and sometimes also scattered glands in other areas, were affected. . . .

"On the other hand, involvement is usually confined to tracheobronchial glands; swelling is rarely marked, and usually only minimal caseation of lymph glands is observed. This is the normal localized reaction in races exposed for generations to the disease.

"There appears, then, to be a definite difference in the reaction of the host in the two instances, and this difference in reaction appears to be associated with differences in resistance of primitive races and races long exposed to the disease.

"These differences in resistance are further substantiated by the fact that the more acute type of pulmonary disease lacking in fibrosis has been observed to be the common condition in the early phase of the Indian epidemic. . . .

"In the acute stage of the epidemic a large proportion of the Indians appeared to have less ability to localize the disease. There is evidence of better localization of the disease in the lungs, and less glandular and generalized disease, in each succeeding generation for the three or four generations during which the Indians of the Canadian plains have been exposed[3]. . ."

"It is evident that:

"(a) In the rising phase of the epidemic, infection was the dominant factor. With the rapid increase in more fatal primary infection in all age groups, increased spreading foci and super-infection pyramiding the summation of all infections as the percentage infected increased on the reserves and in the schools, the disease rapidly assumed the proportions of a plague.

"(b) The factor which guaranteed the survival of the race was resistance. Approximately one-half of the families in a group of 135 families affected with the disease had sufficient resistance to survive even though among surviving families an additional one-fifth of their numbers succumbed to tuberculosis, and a few families escaped mortality from this disease entirely. Among the families that survived the first shock of the epidemic a considerable variation in resistance was noticed.

"(c) Almost universal infection having been approached, the greatest factor increasing the average level of resistance was the elimination of susceptible strains in the tribes and in the families. When the 50% of families who were more susceptible to tuberculosis and other diseases were eliminated, and the excess of native resistant hosts, now limited to new births, was exhausted, the tuberculosis death rate fell from 9000 to 1000 per 100,000 and slowed up in the second generation, falling from 1000 to 800."[4]

By the early 1920's it was evident that the Indian race was to survive, and also that it was in the selfish interest of the white man, for his own protection, to take steps to control tuberculosis in the red man.

It was necessary to arouse public opinion, and this was done, not by any planned campaign, but by the individual efforts of the workers in the various provincial organizations.

Along with this, gradually more medical officers were being appointed: Simes in 1924 to File Hills and Qu'Appelle; E. L. Stone to Norway House in 1926. In 1930 Dr. Stone was moved to Ottawa to head the first *organized* Indian Medical Service.

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A date to record is the year 1933. At that time Dr. George Jasper Wherrett was appointed secretary of the Canadian Tuberculosis Association. Since that time he has been an ardent supporter and wise counsellor in this campaign.

In the period between the two wars particular mention should be made of the outstanding contributions of such workers as the late and much beloved Dr. David A. Stewart, Dr. George Ferguson and Dr. Bert Baker.

During this time surveys were made in British Columbia by Vrooman and Lawler, in Alberta by Baker, in Saskatchewan by Ferguson and Simes; in Ontario, where never-failing support was forthcoming from Clair Brink; in Quebec, where Basil Robertson conducted surveys in Caughnawaga and Frappier assisted, advised and insisted on the use of B.C.G.

The health departments of all of these provinces gave backing and support, and although it must be remembered that these were depression years—"the dirty thirties"—public opinion built up pressure to the point that the government called a "Conference on Tuberculosis Among the Indians of Canada" on June 23 and 24, 1937.

Invited to participate were federal representatives from the Indian Affairs Branch of the Department of Mines and Resources, representatives of provincial health authorities, the Canadian Tuberculosis Association, sanatoria and private physicians with experience in the tuberculosis field.

As acting Minister of the Department of Mines and Resources, the late Hon. C. D. Howe opened the meeting with a touching reference to the then recent death of Dr. D. A. Stewart. The late Mr. John McEachern, Chairman of the Sanatorium Board of Manitoba, was appointed chairman and a comprehensive review was made of the tuberculosis situation as it existed across Canada.

Among the highlights recorded was the fact that about $100,000 had been spent in the previous year on treatment of tuberculosis. It was also announced that a further $50,000 was to be made available, earmarked "T.B. Special". At the close of the conference the following resolution was passed:

> Dr. Fred Jackson (seconded by Dr. Malcolm Bow): "I beg to move that this Council approve the action of the Indian Affairs Branch, Department of Mines and Resources, in holding a conference to discuss the question of tuberculosis among the Indians and trust that the deliberations of this conference will ensure an adequate program for the preservation of the health of the Indians; this program not to be concerned with tuberculosis alone, but should take into consideration venereal diseases, trachoma, and all other conditions which may be a health hazard to the Indians and other residents of the Dominion; and that the Minister of Pensions and National Health be asked to transmit this Resolution to the Minister of Mines and Resources."

In 1937 the Indian death rate for all of Canada was 712 per 100,000 but it is of interest to note that in many areas of the East the rate was below 300 per 100,000. On the prairies, in British Columbia, and among the more primitive bands, mortality rates were from 1000 to 2000 per 100,000.

It was in this era that the so-called "preventorium" in the residential school developed, proving in some instances to be harder to eradicate than the tubercle bacillus.

The 1937 conference gave impetus to a program that was gaining headway when war intervened, with its resultant drastic shortages of professional personnel.

Forward steps were made, however, and a policy of isolating as many cases as possible, whether or not under adequate treatment, was adopted. To this end use was made of existing beds in Federal Government and Mission hospitals of the Northwest Territories.

There follows an extract from the 1939 Annual Report of the Sanatorium Board of Manitoba:

> "During the year one of the landmarks in the fight against tuberculosis in Manitoba among Indians was the purchase by the Dominion Government, Indian Affairs Branch, of the Dynevor Hospital on the banks of the Red River near Selkirk, which was owned and operated for the past forty-three years by the Board of the Anglican Diocese of Rupert's Land. . . . The buildings have been remodelled and refurnished and the hospital will be administered by the Sanatorium Board of Manitoba for the treatment of tuberculosis among the Indians of Manitoba. . . . The Department of Indian Affairs has instituted a constructive program to combat tuberculosis among Indians. If this program is increased from year to year we can look forward to the control of tuberculosis among this susceptible people, and at the same time the removal of a menace to the adjacent white population."

This marked the beginning of a very fruitful partnership wherein the Manitoba Sanatorium Board has operated some federal tuberculosis institutions and co-ordinated the federal antituberculosis program for Manitoba, western Ontario and the central Arctic.

A most significant event was the taking over and remodelling of the Coqualeetza School in 1940 and the opening of it as a 180-bed sanatorium in 1941 with Dr. W. S. Barclay as Superintendent.

During the next year or two a 25-bed unit at Squaw Bay and a 15-bed isolation unit at Manitowaning, Ontario, were acquired and opened. The former institution was supervised by the Fort William Sanatorium.

After VE day it was evident that the war was drawing to a close and that an accelerated plan would be possible. Two meetings of the 1937 Advisory Committee had been held and the Canadian Tuberculosis Association had been asked at their annual meeting in 1944 to reorganize the committee. This was done and as a result Order-in-

Council No. 611 dated January 30, 1945, was passed, as reproduced herewith.

Privy Council
Canada

30 January 1945

The Committee of the Privy Council had before them a report, dated 18th January 1945, from the Minister of Mines and Resources:

"The prevalence of tuberculosis among the Indians in Canada is serious despite the efforts that have been made in recent years to eradicate and prevent the spread of the disease. The present statistics indicate that the Indian death rate from the disease is fifteen times higher than that for the white population.

"Very substantial progress has been made in eradicating tuberculosis from among the white population in Canada and the death rate, not including Indians, has been reduced fifty per cent during the last twenty years. This is largely due to the carrying out of a co-ordinated programme on the part of public and private organizations and has resulted in improved facilities and methods of treatment.

"It is the intention of the Department to embark upon a more active and enlarged programme to eradicate the disease and prevent its spread among the Indians just as soon as the necessary medical and nursing services and other facilities may become available.

"It is desirable to take full advantage of all the knowledge respecting the methods of prevention, detection and after-care, and of the existing facilities that may be available, and to co-ordinate the expanded programme with the programmes now being carried out among the white population of Canada.

"The Canadian Tuberculosis Association has agreed to co-operate with the Department to the fullest extent possible. The Minister therefore recommends that there be set up an Advisory Committee to be called the Advisory Committee for the Control and Prevention of Tuberculosis Among the Indians; that the Committee be composed of not more than twelve members, ten of whom, including the chairman, shall be nominated annually by the Canadian Tuberculosis Association, one member to be nominated by the Department of National Health and Welfare, and one to be a senior medical officer of the Indian Affairs Branch of the Department of Mines and Resources, who shall act as Secretary of the Committee; the first members of the Committee to be the following:

Dr. R. G. Ferguson (Saskatchewan)
Dr. W. H. Hatfield (British Columbia)
Dr. A. H. Baker (Alberta)
Dr. F. W. Jackson (Manitoba)
Dr. G. C. Brink (Ontario)
Col. J. A. Couillard (Quebec)
Dr. P. S. Campbell (Maritime Provinces)
Dr. C. J. W. Beckwith (Maritime Provinces)
Dr. C. W. MacMillan (Maritime Provinces)
Dr. P. E. Moore, Indian Affairs, Secretary
Maj. Gen. G. B. Chisholm, Department of National Health and Welfare
Dr. G. J. Wherrett, Executive Secretary, Canadian Tuberculosis Association

"The Minister further recommends:

"1. That the first meeting of the Committee shall be called by the Minister of Mines and Resources and at such meeting a Chairman and Secretary shall be chosen; thereafter the Chairman shall be the person nominated by the Canadian Tuberculosis Association and the Secretary shall be the representative of the Indian Affairs Branch.

"2. That the Committee shall meet from time to time at the call of the Secretary and if possible not less than once every year.

"3. That the Committee shall have authority and will be expected to inquire into the present methods of tuberculosis prevention, detection, treatment and after-care or supervision of the Indians, and report thereon and make recommendations from time to time to the Minister of Mines and Resources with a view to:

1. Assisting the Indian Affairs Branch in making the best use of the facilities available.
2. Improving these facilities.
3. Correlating the antituberculosis work of the Indian Affairs Branch with similar services of the Provinces and other departments of the Federal Government.
4. Making the best possible use of the monies included in the annual parliamentary vote or votes for the purpose of eradicating and preventing the spread of the disease among the Indians.

(*signed*)

A. D. P. HEENEY,
Clerk of the Privy Council"

The first meeting of the Committee was called for May 30 and 31, 1945, and in addition to the Committee was attended by Col. J. D. Adamson, Major Geo. Northwood, chairman of the Manitoba Sanatorium Board, and Drs. E. L. Ross, Barclay, Simes, Falconer, Crombie, Bow and Keeping.

The verbatim report of this meeting is 218 pages of most interesting reading.

The Advisory Committee reviewed the Indian tuberculosis problem in each province and in the Northwest Territories, and estimates of bed requirements were made. The U.S. Army Hospital at Edmonton, destined to become the Charles Camsell Indian Hospital, was mentioned as a possibility.

During the latter years of the war, a Committee on Wartime Hospitals and Hospitalization was formed, of which the writer was a member, to coordinate hospital construction. Then and subsequently, this committee was charged with recommending the disposal of surplus hospitals. Thus, even before Armistice Day, Indian Health Services had acquired a 180-bed hospital at Miller Bay near Prince Rupert, B.C., built for the R.C.A.F. but never operated by them, and a 160-bed U.S.A.F. hospital at Clearwater Lake near The Pas, Manitoba.

The committee made many concrete recommendations to improve medical and survey coverage, among which were recommendations to increase the number of full-time federally appointed medical officers and the appointment of provincial senior medical officers. From these recommendations grew the system of regional and zone administration presently employed by Indian and Northern Health Services.

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By 1945 there were over 900 Indians under treatment across Canada and the government was spending over $1,000,000 annually on tuberculosis control. The death rate had dropped to 564.5 per 100,000.

In quick succession the Department of Mines and Resources acquired National Defence hospitals for Indian health work: at Edmonton 500 beds, Nanaimo 220 beds, Brandon 200, North Battleford 60. Fort Qu'Appelle, of course, had been in operation with about 80 beds since 1936.

November 1, 1945 is another significant date, for on that day an Order-in-Council became effective which transferred the medical care of Indians and Eskimos from the Department of Mines and Resources to the newly formed Department of National Health and Welfare of which the Hon. Brooke Claxton was Minister and Dr. Brock Chisholm, Deputy Minister. The segment of the department concerned with the transfer of responsibility was to be known as the Indian and Eskimo Health Services directorate.

The story of the years 1945 to 1960 is one of steadily increasing budgets, expanded and improved facilities and administration. This enabled an all-out attack on tuberculosis and a control program in all its phases, including case finding, prompt and effective treatment, vaccination and rehabilitation. Worthy of mention in the field of prevention is the co-operation of the Indian Affairs Branch of the Department of Citizenship and Immigration. This has resulted in a program of supplementary food rations for all the members in a tuberculous patient's family, for six months after the case has been found and the patient removed to sanatorium and for six months after he returns from sanatorium.

In these 15 years, hospitals were built at Sioux Lookout and Moose Factory; Fort Qu'Appelle was enlarged; a 90-bed wing was replaced at Coqualeetza, and a whole chain of nursing stations was constructed across the country, including the Arctic.

An organized public health nursing service has been developed, and one of its major responsibilities is the follow-up of cases and contacts.

The Parc Savard Hospital in Quebec City was at one time used to capacity and plans were made to open two other hospitals, Rockhead in Halifax and the former naval hospital at St. Hyacinthe, Quebec. When it became evident that existing beds would meet Indian health needs, these plans were abandoned.

Now, like other agencies, Indian and Northern Health Services finds itself closing hospitals and converting tuberculosis beds to beds for general hospital care. Parc Savard, Squaw Bay and Dynevor have been closed and the 200 beds at Brandon are being used for other purposes.

It is of passing interest to note that the same dread disease that almost annihilated the Indians of the plains also threatened the extinction of the buffalo which had been their traditional staff of life. Only prompt action by the Wild Life Division of what is now the Department of Northern Affairs and National Resources prevented this. The buffalo were moved from Wainwright to Wood Buffalo Park where annually they are corralled in numbers of up to 2000 at a time, given tuberculin tests, and retained for 72 hours; animals found infected are marked for immediate slaughter. This program is showing results in a very much lowered incidence of the disease.

The public health campaign amongst Eskimos has been equally vigorous and successful. All evidence points to the fact that they have been well tuberculized for several generations, probably getting their original infection from the early whalers.

The Indian Advisory Committee still functions and is now customarily formed from the members appointed each year to the Canadian Tuberculosis Association Management Committee.

It is through the combined efforts of many—including Indian and Northern Health Services, provincial organizations and the Canadian Tuberculosis Association—that the point has been reached where it can be said of the tubercle bacillus that it is now "no longer captain!"

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

The draft of a bill which has been prepared on behalf of the board of governors of the University of Toronto has been placed in the hands of the medical members of the Ontario legislature. The purpose of the bill is to abolish the examinations that the medical graduates of the university have been compelled to take before the council. The bill is now before the provincial cabinet, but will not be taken up by the government until the views of the medical council, Queen's, and the Western universities, and the doctors of the province, have been heard. The final clause provides that any other university may secure the same privilege if the council declares that its standard is equal to that of Toronto University.—*Canadian Medical Association Journal*, 1: 364, April 1911.

CASE REPORTS

COMPLETE ATRIOVENTRICULAR BLOCK COMPLICATED BY ADAMS-STOKES SEIZURES SUCCESSFULLY TREATED WITH ISOPROPYL NORADRENALINE (ISUPREL)*

JONG K. LEE, M.D.,† *London, Ont.*

EMERGENCY treatment is necessary when complete heart block is associated with recurrent attacks of Adams-Stokes seizure. Although direct thumping of the left precordium may restore the heart beat in ventricular standstill, as a rule, more definite measures must be taken to control the attacks of Adams-Stokes syndrome.

The introduction of an artificial cardiac pacemaker for patients with ventricular standstill and Adams-Stokes attacks appears[1, 2] to be a major achievement. However, adrenaline hydrochloride and isopropyl noradrenaline remain the drugs of choice for treatment of this emergency. Nathanson and Miller[3-5] advocated the use of isopropyl noradrenaline, which they consider to be more effective than adrenaline hydrochloride, in the treatment of Adams-Stokes attacks.

A 77-year-old male was admitted to hospital at 11.30 a.m. on June 29, 1960, with a diagnosis of complete heart block. He had had diabetes for 15 years which was apparently kept under adequate control by protamine zinc insulin, 20 units per day, and a low-calorie diabetic diet.

During the night of June 21 he developed severe retrosternal chest pain radiating to both arms and lasting throughout the entire night. The next morning he fainted and collapsed on the street on his way to work. He was taken by ambulance to the emergency department of another hospital where a blood sugar determination and urinalysis were carried out. The results were found to be normal and he was sent home. He continued to feel weak and dizzy until June 28, when he was seen by an internist who noted a pericardial friction rub and a blood pressure of 125/85 mm. Hg, with a pulse rate of 80/min. The next morning (June 29) he experienced a syncopal attack with loss of consciousness for approximately two minutes, at home.

On admission to hospital after the syncopal attack, his heart rate was 28/min., and blood pressure 95/45 mm. Hg. He did not appear to be in shock. Auscultation revealed some moist rales at the left base but no cardiac murmur or friction rub. The neck veins were engorged and pulsating with the patient in a 45° reclining position. His blood sugar level was 474 mg. %, with 3+ glucose and a trace of albumin but no acetone in the urine.

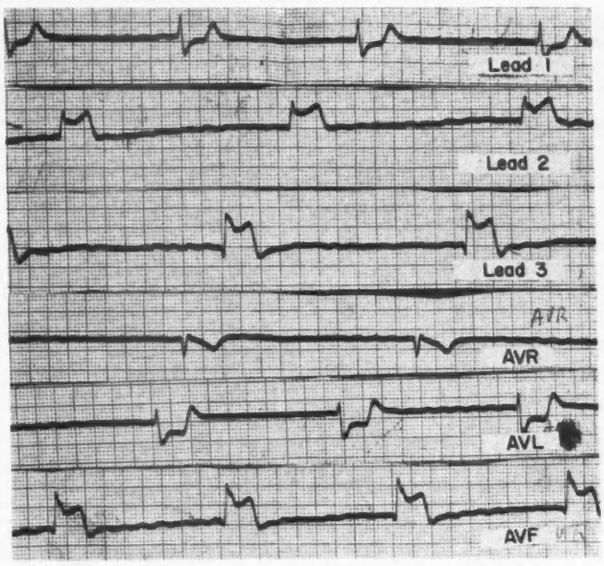

Fig. 1.—The tracing taken at approximately 12.50 p.m. reveals auricular fibrillation, complete A-V block and acute posterior myocardial infarction. The precordial leads revealed a deep S-T segment depression but no Q wave.

The electrocardiogram (Fig. 1), taken at 12.50 p.m., revealed the pattern of acute posterior myocardial infarction, auricular fibrillation and complete auriculoventricular block with a ventricular rate of about 28/min. Around 1 p.m. the patient developed typical recurrent Adams-Stokes seizures with intervening short intervals of consciousness.

The first episode was terminated in two or three minutes by thumping the patient's precordium a few times. This attack was characterized by the sudden onset of unconsciousness, pallor, a fixed upward deviation of the eyes and irregular twitching movements of both arms, followed by profuse perspiration and return to a clear mental state. The electrocardiogram taken during one of these attacks revealed complete ventricular standstill. After he had regained consciousness, he was given one sublingual tablet of isopropyl noradrenaline (10 mg.). However, he again developed a series of four short Adams-Stokes attacks, each lasting approximately 30 seconds, with intervals of consciousness of one or two minutes. The second attack developed about seven minutes after the isopropyl noradrenaline sublingual tablet had been administered. The last four seizures were abolished either spontaneously or by thumping his precordium.

At 1.10 p.m., intravenous isopropyl noradrenaline, 1 mg. in 500 c.c. of 5% glucose solution, was administered along with nasal oxygen. When the rate of intravenous infusion of isopropyl noradrenaline was gradually increased to 30 to 40 drops per minute, the electrocardiogram (Fig. 2) revealed a greatly increased ventricular rhythm with a rate of 100/min. At 1.15 p.m. the infusion of isopropyl noradrenaline was discontinued because of tachycardia (Fig. 3a), after 0.2 mg. had been administered in this manner.

The patient developed no subsequent recurrence of Adams-Stokes attacks without further administration of isopropyl noradrenaline. The electrocardiogram taken at 8 p.m. (Fig. 3c) revealed a sinus rhythm with first-degree heart block. The subsequent electrocardiograms

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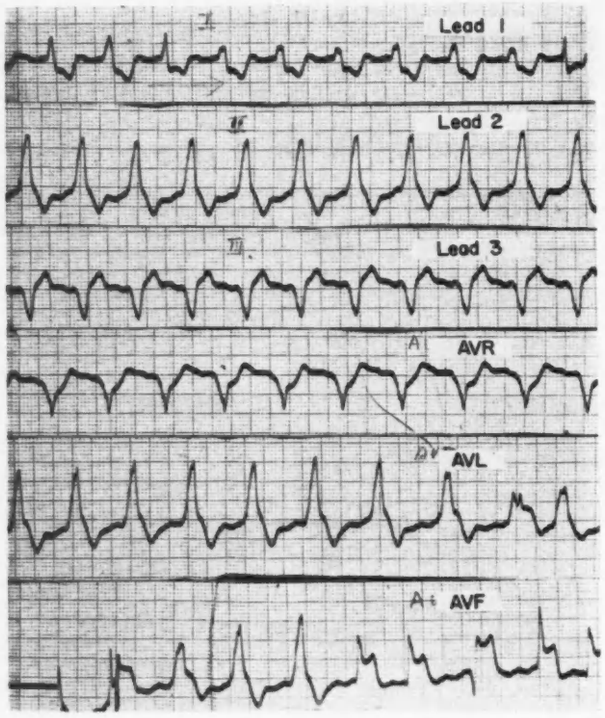

Fig. 2.—ECG, taken at approximately 1.10 p.m. after administration of isopropyl noradrenaline (Isuprel) by intravenous drip, reveals a pattern of slow ventricular tachycardia at a rate of 100 per minute. The QRS complex is deformed and widened with deflection in lead III suggesting that the pacemaker is in the right bundle.

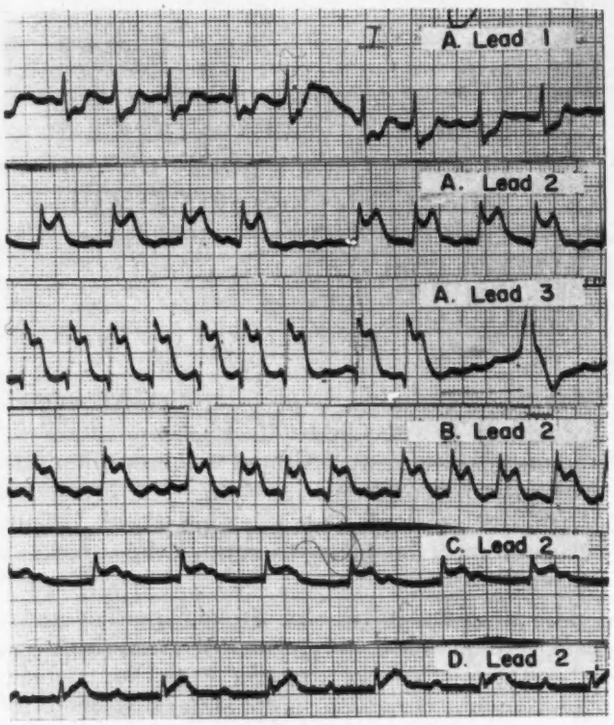

Fig. 3.—(a) The ECG taken at approximately 1.15 p.m. reveals a run of ventricular tachycardia with a rate of 150 per minute. The deflection of the QRS complex is upward in lead III, suggesting a shift of the pacemaker from the tracing in Figs. 1 and 2. (b) ECG taken at 1.18 p.m. after discontinuation of isopropyl noradrenaline infusion. (c) ECG taken at 8 p.m. shows conversion to sinus rhythm with a P-R interval of 0.56 second which became gradually shorter on successive recordings. (d) The ECG taken on the following day reveals shortening of the P-R interval.

all revealed a progressive shortening of the P-R interval and sinus rhythm. He was sent home from hospital in a satisfactory condition after four weeks of medical management. Subsequently he was followed up at the medical clinic without any further recurrence of heart block or Adams-Stokes seizure.

HISTORICAL REVIEW

In 1761 Morgagni briefly reported two cases of epileptiform or pseudoepileptic attacks associated with a slow pulse and syncope.[6] Adams (1827) described a patient whose pulse rate was 30/min. and who suffered from dyspnea, cough and attacks of fainting. Considerable attention was drawn to this subject by Stokes who published (1846) reports of four patients with permanent slow pulse. It has been reported that the underlying mechanisms responsible for the production of Adams-Stokes syndrome include ventricular standstill, ventricular tachycardia, ventricular fibrillation or a combination of these, and, on occasion, an extreme bradycardia with complete heart block.[7]

An analysis of 71 cases of complete A-V block by Ide[8] revealed that 41 were associated with coronary arteriosclerosis, including patients with hypertensive heart disease and acute myocardial infarction (eight cases). Cardiac glycosides (12 cases) were the second commonest cause in Ide's series, followed by congenital heart block, rheumatic heart disease, scarlet fever, syphilis, diphtheria and hyperthyroidism in that order of frequency. Hudson, Chobanian and Relman[10] described the occurrence of chronic heart-block complicated by Adams-Stokes attacks produced by hyperpotassemia due to primary hypoaldosteronism. The author has encountered a case of myxedema associated with complete A-V block and Adams-Stokes disease. In the case reported above, the etiology appeared to be acute posterior myocardial infarction due to coronary thrombosis.

Willius[11] reported two cases of Adams-Stokes seizures treated successfully by thyroxin. However, Nathanson and Miller's study[4] indicated that thyroxin, digitalis, caffeine, Coramine, Metrazol, barium chloride and calcium chloride are therapeutically ineffective, whereas adrenaline and its related drugs effectively increased the rhythmic function of the heart. Isopropyl noradrenaline is closely related to adrenaline and noradrenaline. It differs in that an isopropyl group is substituted for the methyl group in adrenaline. Like adrenaline, isopropyl noradrenaline increases the cardiac rate, the stroke volume, the amplitude of myocardial contraction and the coronary blood flow.

In a comparative study of noradrenaline, adrenaline and isopropyl noradrenaline, it was found that the latter had little or no pressor action, but possessed a quality that is highly desirable in any drug used for prevention or treatment of sudden inactivity of the heart, in that it is effective in overcoming cardiac standstill without any tendency to induce ventricular fibrillation.[4, 5] Isopropyl noradrenaline is five times more active than adrenaline when administered subcutaneously. It

increases the rate of the cardiac pacemaker considerably and relocates the pacemaker in the vicinity of the A-V node in cases of complete A-V block.[12]

It is important to obtain electrocardiographic tracings to be certain that asystole is due to ventricular standstill and not to ventricular tachycardia or fibrillation, because adrenaline and its related compounds may cause a transient arrhythmia to become permanent and fatal.[5] Schwartz and Schwartz[13] studied the effects of isopropyl noradrenaline on 10 patients with Adams-Stokes syndrome, during the presence of normal sinus rhythm and transient heart block. In all 10 patients, it was possible to convert a transient partial or complete heart block to normal sinus rhythm by the administration of this drug, but in five of the 10 patients it was impossible to maintain normal rhythm for any length of time. However, it was also observed in the same study that in two patients, at a time when they were free from syncopal seizures and when their cardiac rhythm revealed 2:1 heart block, the use of isopropyl noradrenaline resulted in a further transitory reduction in the ventricular rate with associated Adams-Stokes "seizure". This phenomenon was felt to be due to the presence of "labile state".

DISCUSSION

The therapeutic value of isopropyl noradrenaline in the treatment of Adams-Stokes attacks has been confirmed by many workers. Chandler and Clapper[14] successfully used 20-mg. doses of this drug by the sublingual route in the treatment of such attacks due to complete heart block. Its intravenous infusion was effective in maintaining a normal heart rate in one case. It was also observed by the same authors that doses as large as 10 to 100 times the recommended dose could be given without untoward effect. Schumacher and Schmock[12] were also able to abolish Adams-Stokes attacks by subcutaneous administration of isopropyl noradrenaline. Adelman, Kravitz and Gouley[15] reported a marked symptomatic improvement in two patients when the method of administration was changed from the sublingual to the subcutaneous route. It is worthy of note that, in the case reported here, one 10-mg. tablet administered sublingually did not prevent further attacks, though the tablet had not been completely dissolved when these recurred. It requires over seven minutes for a sublingual tablet of isopropyl noradrenaline to dissolve completely; therefore, rapid action of the drug is not to be expected when it is administered in this way.

A case of complete A-V block with Adams-Stokes seizures treated with intravenous isopropyl noradrenaline 1 mg., together with an artificial pacemaker, has been reported.[16] Gale and Enfroy[17] also reported a case successfully treated by the continuous infusion of 20 mg. of this drug in one litre of glucose solution. This technique of continuous intravenous administration appears to be a highly satisfactory form of treatment for patients with recurrent attacks of Adams-Stokes seizure.

It has been said that isopropyl noradrenaline acts predominantly on the higher centres of cardiac impulse production (sinus and atrioventricular node[4, 9]); therefore it does not appear to predispose to ventricular tachycardia or fibrillation.

In the case described in this report, however, the deflection of QRS complex in lead 3 (Fig. 2) indicates that the pacemaker had shifted below the atrioventricular node. It is interesting to note the conversion of auricular fibrillation to sinus rhythm with the administration of isopropyl noradrenaline. Progressive shortening of the P-R interval also has been noted by others. Intravenous administration of isopropyl noradrenaline appears to have prevented a further attack of Adams-Stokes seizure during the crucial period in this patient's case.

SUMMARY

A case of recurrent Adams-Stokes seizures with complete atrioventricular block after posterior myocardial infarction, successfully treated by the intravenous administration of isopropyl noradrenaline (Isuprel) solution is reported. The rapid intravenous infusion of diluted isopropyl noradrenaline solution precipitated a transient episode of ventricular tachycardia which has not been described by others. The therapeutic value of the intravenous administration of isopropyl noradrenaline in the management of recurrent Adams-Stokes attacks due to ventricular standstill is discussed.

I am indebted to Dr. G. W. Manning, Associate Professor of Medicine, University of Western Ontario, London, for his encouragement and criticism in the preparation of this article.

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CARPAL TUNNEL SYNDROME CAUSED BY AN UNUSUAL CONGENITAL ANOMALY

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J.W., A HUSKY 19-year-old uranium miner, noticed a lump on the flexor aspect of his right wrist in 1957. This was first observed after a period of rapid growth and muscular weight gain, and was most obvious when the wrist and fingers were fully flexed. In 1958, while doing heavy labour, he noticed that his fingers would "go to sleep" if he clenched his hand forcibly with the wrist extended. Seeking medical aid, he was told that it was most likely a cyst, which would ultimately require treatment.

His symptoms progressed to the point that the numbness persisted minutes after his grip was relaxed, and the burning dull pain accompanying it had become more pronounced. No definite weakness was noted.

He again sought medical aid, and hypoesthesia and paresthesia over the median nerve distribution were clearly demonstrated, but there was no muscle wasting or weakness. The lump, which the patient stated had recently become enlarged, was very evident when the wrist was flexed and the fingers were forcibly flexed, seemingly rising out of the depths of the flexor surface of the wrist immediately radial to the flexor carpi ulnaris tendon and just proximal to the transverse carpal ligament. The 3 cm. x 3 cm. mass was rounded, rubbery and non-tender. No tenderness or paresthesia could be elicited over the carpal tunnel.

A provisional diagnosis of synovial cyst was made and it was elected to explore the wrist to obviate permanent median nerve damage.

In December 1959, using general anesthesia, Cheyne technique, Esmark bandage and tourniquet, a 3″ transverse incision was made over the swelling and was carried down through the deep fascia to the mass. The latter was seen to consist of muscle lying immediately radial to the flexor carpi ulnaris tendon, directly volar to the ulnar vessels and nerve, and ulnar to the median nerve which lay under a well-developed palmaris longus tendon. It consisted of the deep portion of flexor digitorum sublimis supplying the fifth finger, but which, anomalously, was composed of muscle fibre rather than tendon, extending well into the carpal tunnel. The carpal tunnel was not opened into the hand, so the distal limit of the muscular portion of the structure was not defined.

With the little finger pulled into flexion by traction on the muscle and the wrist flexed, the muscle was severed and tagged with black silk. A very wide belly occupied a good portion of the carpal tunnel, and the transection was carried out distal to this belly. The carpal tunnel itself was not explored, the anomalous muscle mass being considered an adequate cause of median nerve compression in this case.

The rationale of muscle transection was as follows: (1) Very minimal if any functional deficit would be caused by severing this portion of the flexor digitorum sublimis. (2) The main space-occupying muscle mass would then contract into the forearm. (3) The remaining distal portion without innervation would have no contractility to compress the nerve and would eventually atrophy.

Postoperatively this patient did well, and to date has had no further symptoms, nor has any weakness resulted from transection of this portion of the flexor digitorum sublimis.

DISCUSSION

Tanzer[1] in a report of 34 hands affected by the carpal tunnel syndrome described one case with features similar to those of the patient reported here. Bunnell[2] also reported one case of carpal tunnel syndrome arising from "an abnormally low muscle belly of the sublimis of the long finger contracting against the nerve". Wood Jones,[3] in his "The Principles of Anatomy as Seen in the Hand", describes the marked variability of the deep portion of the flexor digitorum sublimis, arising from the medial condyle of the humerus and normally giving way to a tendinous structure in midforearm. From this tendon two secondary bellies arise and terminate in the flexor digitorum sublimus tendons to the index and fifth fingers.

SUMMARY

A case of carpal tunnel syndrome in a 19-year-old male is described. The cause of median nerve compression was an anomalous medial belly of the flexor digitorum sublimis which was contracting on the nerve in the carpal tunnel.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

GOVERNMENT LABORATORIES

Few persons appreciate the extent and value of the scientific work which is being carried on at the government laboratories in Ottawa. From the beginning, even so technical a subject as bacteriology has had its place; but, since Mr. Lehmann left the staff to accept an appointment under the government of Burmah, this important method of investigation has been in abeyance. On February 4, one of the buildings of the Department of Inland Revenue was destroyed by fire. In the reconstruction the needs of bacteriology will be met, and Mr. Aimé Valin, who for many years was in the department of chemistry, has been engaged for the work.

It might be proper to consider if the time has not come for establishing a closer correlation between the various laboratories. – Excerpt from editorial, *Canadian Medical Association Journal*, 1: 262, March 1911.

SPONTANEOUS FRACTURE DISLOCATION OF THE STERNUM

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THIS CASE is being reported for a number of reasons:

1. Spontaneous fracture of the sternum has been reported only once previously in the medical literature and in that instance it was at a different site. It was produced by coughing, and there was no displacement requiring reduction.[1]

2. Thoracic cage injuries sustained in steering wheel accidents are usually those of numerous rib fractures, with a resultant general sternal instability. One case of a similar type of deformity localized in the sternum, without rib injury, has been reported from a steering wheel accident, and this also has occurred at a somewhat lower site.[2]

3. This fracture dislocation was produced solely by muscular violence during a gymnastic exercise.

4. Operative reduction of the deformity was carried out in conjunction with a pacemaker and defibrillator using arm and chest leads.

S.M., an 18-year-old high school gymnast of considerable talent, was performing an exercise known as "back uprise" on the parallel bars at the high school gymnasium on the morning of October 13, 1959. This exercise consists of the following maneuvers:

a. With the hands grasping the parallel bars, one hand on each, and with the forearm and arms lying along the top of each bar respectively, the weight of the body is supported, with the feet swinging free, by the whole of each arm from the hand to the arm-pit.

b. With the axilla as a pivot point, the feet and body are swung forward approximately 45°.

c. The feet and body are then swung backward through 90°.

d. At the height of the backward swing, and while still keeping the arms straight, the gymnast by sudden contraction of the pectoralis and latissimus muscles thrusts the body now upwards and forwards so that he is supporting himself now on the parallel bars only by his hands with the arms extended in the vertical position and the body also vertical, parallel to the arms.

It was during phase "d" of the above maneuver that the patient experienced sudden severe pain in the midline of the upper chest. He was forced to drop from the bars and he was unable to move. He was brought immediately to the emergency department of McKellar General Hospital, Fort William, Ont., where he was first seen.

At the time of his initial examination he was complaining of severe pain at the site of the sternal angle of Louis and this was aggravated by each breath. He was somewhat pale and sweating. He had bradycardia with a pulse rate of 60. His blood pressure was 130/84 mm. Hg. The pulse was of excellent volume. Respirations were shallow, and the rate was 26 to 30 per minute. The respirations were completely abdominal in type. There was an obvious deformity at the junction of the manubrium sterni with the superior sternebra of the gladiolus. The inferior border of the manubrium was dislocated posteriorly to the superior border of the first sternebra. The patient was taken to the x-ray department where radiological examination confirmed the dislocation.

Because of the bradycardia it was postulated that the posterior dislocation of the manubrium might be causing sufficient pressure on the mediastinal contents to bring about vagal slowing of the heart rate. For this reason it was thought that reduction of the deformity might, by sudden removal of the slowing influence, allow rebound tachycardia which could give rise to ventricular fibrillation. Since there was no previous experience with this type of deformity to assist us, it was decided to reduce the deformity under general anesthesia with the cardiac defibrillator and the cardiac pacemaker attached to the patient through arm and chest leads.

The reduction proved to be exceedingly simple and was performed under endotracheal anesthesia with the patient in the supine position. A median vertical incision was made across the site of the deformity. The bones of the deformed joint were demonstrated readily. The inferior border of the manubrium was dislocated posteriorly in relation to the superior border of the first sternebra, as was expected from the clinical and radiological examinations. In addition there was a complete tear of the anterior joint capsule and a triangular fracture not seen on the radiograph, a fragment measuring 2 cm. x 1 cm. off the right inferolateral angle of the manubrium. There was no evidence of any disease process in the bone or joint. The second costal cartilages remained with the first sternebral segment on each side.

Two small drill holes were made into the body of the manubrium side by side, so that the prongs of an ordinary towel clip could be placed through the drill holes to grasp the manubrium. It was then elevated with ease into its normal position. Simultaneously with this maneuver the heart rate increased to 90 and the blood pressure fell to 100/70 mm. Hg, but within one minute the blood pressure returned to normal and the heart rate stabilized at 76. Fixation of the fracture dislocation was carried out by means of a mattress-type suture using No. 25 stainless steel wire. The fractured portion of the manubrium reduced with the manubrial fragment, and required no special treatment. The capsule of the joint was then sutured with No. 2 chromic catgut. The patient returned to the ward to lie supine on a firm mattress with fracture boards.

Forty-eight hours postoperatively the patient was further immobilized by means of a figure-8 axillary type bandage of flannelette, applied in the manner sometimes used in the treatment of a fractured clavicle. The patient was then allowed to be ambulatory. For the first 48 hours he suffered considerable discomfort at the site of the injury, but as soon as he became ambulatory the pain lessened. His postoperative course was excellent and he was discharged from hospital on October 27, two weeks after the injury was sustained.

The figure-8 bandage was permanently removed on November 3. He began normal physical training activities in school in January 1960, and he returned to gymnastic activities including the back uprise in February 1960, four months after his injury. He has been able to do this maneuver without discomfort or other incident.

SUMMARY

A fracture dislocation of the sternum at the sternomanubrial joint by muscular violence is reported for the first time.

The mode of production of the injury was the sudden thrust of the whole weight of the body to the outstretched arms in a gymnastic procedure, the arms rising from the horizontal to the vertical position at the moment of thrust.

A simple means of immediate reduction and fixation, easily performed, which achieves anatomical correction, has been carried out and proved adequate.

Bradycardia, presumably due to pressure of the posteriorly dislocated fragment upon the mediastinal contents, disappeared immediately upon reduction of the deformity and was replaced by mild sinus tachycardia which subsided spontaneously within one minute.

The patient was able to perform the same gymnastic procedure four months later without incident.

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SHORT COMMUNICATION

IN VITRO SENSITIVITY OF ROUTINE HOSPITAL PATHOGENIC BACTERIA TO A GROUP OF COMMONLY USED ANTIBIOTICS

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THE WIDE variation in sensitivity of bacteria to any given antibiotic from one community to another is well recognized. It is the purpose of this paper to report the results of a survey of routine bacterial sensitivity testing at a 385-bed hospital serving a city of 41,000 and its surrounding community.

MATERIAL AND METHODS

The records of bacterial sensitivities reported during a six-month period in 1960 at the St. Catharines General Hospital were examined. The fact that eventual publication of the results of these tests was not contemplated at the time they were performed minimizes the element of bias. All organisms were not tested against each antibiotic in this series, since routine procedures were not changed in any way. Thus, where 100% resistance is known to exist (e.g. *E. coli* resistance to penicillin), such organisms were not tested with antibiotics to which they were known to be resistant.

The antibiotics used in this series were chloramphenicol, erythromycin, novobiocin, a commercially available novobiocin-tetracycline combination,† oxytetracycline, penicillin and tetracycline. The standard disc plate method of testing was employed. The strengths of the discs used were as follows:

Chloramphenicol	30 μg./disc
Erythromycin	15 μg./disc
Novobiocin	30 μg./disc
Novobiocin-tetracycline combination	15 μg. novobiocin + 15 μg. tetracycline /disc
Oxytetracycline	30 μg./disc
Penicillin	10 units/disc
Tetracycline	30 μg./disc

RESULTS

The total results of sensitivity testing with these seven antibiotics are recorded in Table I.

TABLE I.

	Total number of strains tested	*% of strains sensitive*
Chloramphenicol	595	74.7%
Erythromycin	338	59.7%
Novobiocin	211	82.5%
Novobiocin-tetracycline combination	613	89.2%
Oxytetracycline	413	44.7%
Penicillin	247	44.5%
Tetracycline	552	66.7%

The results were then tabulated with reference to the individual sensitivity of an organism to each individual antibiotic, as shown in Table II.

DISCUSSION

Several interesting facts are indicated by these data. The effectiveness of the combination of novobiocin and tetracycline together, when tested with discs containing 15 μg. of each antibiotic, was greater than that observed when either antibiotic was tested alone using discs with 30 μg. of antibiotic per disc. Thus, the combination was effective in 89.2% of tests in this series, whereas novobiocin alone was 82.5% effective, and tetracycline alone only 66.7% effective. It is considered that the figure for novobiocin is somewhat high owing to the fact that, in keeping with the routine procedure in this laboratory, novobiocin was not tested against *E. coli*

*Director of Laboratories, St. Catharines General Hospital.
†Albamycin T (Upjohn).

TABLE II.

Organism		*Chloramphenicol*	*Erythromycin*	*Novobiocin*	*Novobiocin-tetracycline combination*	*Oxytetracycline*	*Penicillin*	*Tetracycline*
Staphylococcus	Number of strains	212	209	128	207	164	133	205
	% sensitive	80.6%	66.0%	93.8%	99.5%	41.5%	21.8%	68.8%
E. coli	Number of strains	73			69	36		71
	% sensitive	80.8%			69.6%	27.8%		60.6%
Proteus species	Number of strains	55			63	41		49
	% sensitive	65.5%			84.1%	4.9%		48.8%
Pseudomonas species	Number of strains	57	22		65	46		63
	% sensitive	42.1%	18.1%		70.8%	37.0%		36.5%
Aerobacter aerogenes	Number of strains	32			31	25		32
	% sensitive	65.5%			87.1%	48.0%		65.6%
Streptococcus species	Number of strains	62	26	26	73	40	34	54
	% sensitive	87.1%	84.6%	92.3%	95.9%	82.5%	85.3%	92.6%
Diplococcus pneumoniæ	Number of strains	33	29	22	37	19	36	29
	% sensitive	100%	100%	100%	100%	100%	100%	100%
Neisseria species	Number of strains	13			15	8	14	10
	% sensitive	100%			100%	87.5%	71.4%	100%
Klebsiella pneumoniæ	Number of strains	22	4	9	26	18	4	12
	% sensitive	68.2%	0%	28.5%	80.8%	55.6%	0%	63.6%
Hemophilus species	Number of strains	7	4	2	6	5	3	3
	% sensitive	100%	100%	100%	100%	80%	100%	100%
Paracolobactrum species	Number of strains	5			4	4		5
	% sensitive	80%			75%	50%		60%
Miscellaneous	Number of strains	3			4	4		1
	% sensitive	66.6%			75%	75%		0%

or strains of Proteus or Pseudomonas, whereas both the novobiocin-tetracycline combination and tetracycline alone were tested against these organisms.

The results of a study carried out in the United Kingdom and reported by Goodier and Parry in 1959[1] are similar to those described in this report. The percentage of all organisms tested that were sensitive to chloramphenicol (74%) was identical in the two studies. The percentages of organisms sensitive to tetracycline were similar (60% vs. 66%), as were those for erythromycin (55% vs. 59%). However, Goodier and Parry reported that in their series penicillin was only 23.3% effective, whereas in the study reported in this paper it was 44.5% effective. The novobiocin-tetracycline combination was not employed in the investigation described by Goodier and Parry.

Further significant data emerge from analysis of the results of sensitivity testing of individual organisms. In the case of staphylococci, only one of 207 strains was resistant to the novobiocin-tetracycline combination; 83.8% of staphylococci were sensitive to novobiocin alone; 80.6% of staphylococci were sensitive to chloramphenicol. These figures confirm those of another recent Canadian study at present in preparation for publication.[2] Penicillin is becoming progressively less effective in staphylococcal infections, as was shown by the fact that only 21.8% of strains of staphylococci were sensitive to penicillin.

In the case of *E. coli*, chloramphenicol was the most effective antibiotic. However, when Proteus, Pseudomonas and *Aerobacter aerogenes* were considered, again the combination of novobiocin-tetracycline was superior.

In streptococcal infections, all seven antibiotics were effective *in vitro* in from 82.5% to 95.9% of the tests in this study.

SUMMARY

Results of routine sensitivity testing of commonly encountered organisms by the disc plate method at the St. Catharines General Hospital in 1960 are reported. The most effective preparation tested was a combination of novobiocin and tetracycline to which 89.2% of 613 organisms were sensitive. On the basis of *in vitro* studies, this combination was also superior to the other six antibiotics in this series when tested against staphylococci, streptococci and strains of Proteus, Pseudomonas and *Aerobacter aerogenes*.

Mr. C. J. Marston, technician in charge of bacteriology, St. Catharines General Hospital, performed the laboratory tests on which this report is based.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

The press despatches which appeared at the time the "Roddick Bill" was under consideration at Ottawa, did some injustice to the profession in Saskatchewan. It was made to appear that the opposition in that province was so strong that the Bill should not be reported. From the *Western Medical News* we are glad to learn that "it is well known that a very large majority of the profession in Saskatchewan is favourable to the Roddick Bill." It is a matter for congratulation that the Bill has now been passed into law with the full consent and approval not only of a majority but of all the provinces.—*Canadian Medical Association Journal*, 1: 459, May 1911.

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CIGARETTE SMOKING, LUNG CANCER, AND THE MEDICAL PROFESSION'S RESPONSIBILITY

A RELATIONSHIP between cigarette smoking and bronchogenic carcinoma has been recognized for many years and has been officially acknowledged by many responsible medical organizations. The formidable array of clinical, epidemiological, experimental, chemical and pathological evidence supporting this relationship must surely have had some effect on the thinking of the physician and the advice he gives his patients. In spite of this, the sale of cigarettes in Canada in 1960 totalled 34,289,354,000—an increase of 1.4% over the previous high in 1959. With the help of advertising budgets which increase year by year, the public is bombarded by "land, sea and air" through every possible medium of communication with material which extols the benefits conferred by cigarette smoking on both mind and soul. Our favourite television heroes, our most glamorous video queens, the host of highly intellectual panelists, all or almost all are seen daily and nightly through a haze of swirling cigarette smoke. Programs specially designed for family viewing not only feature cigarette smoking by almost everyone in the story over the age of puberty, but are liberally sprinkled with cigarette commercials by their eager sponsors.

Early in 1960, the Board of Directors of the American Cancer Society issued a statement agreeing with the evidence of a cause-effect relationship of cigarette smoking and lung cancer and stating that "all organizations and agencies concerned with cancer have a responsibility to formulate programs of action . . . in order to reduce the incidence of this 'largely preventible' disease." Public health programs designed to reduce the incidence of cigarette smoking have proved to be anything but successful. Where accurate statistics are available, approaches through normal health educational channels have evidently failed. In reviewing the reports, most of them from Britain, it would seem that attempts to alter public smoking habits have failed for two main reasons:

1. The approach has been to the confirmed adult smoker rather than to the school child who is trying his first puff.

2. The medical profession has failed to lead the way. They have had, and still have, an opportunity to demonstrate their support of an important advance in preventive medicine by setting an example to the lay public and by announcing, vocally and in print, their belief as informed individuals that cigarette smoking is a major factor in the etiology of bronchogenic cancer.

The report from the City of Winnipeg Health Department published in this issue indicates a sincere attempt to influence the smoking habits of school children by a planned program of health education directed at an age group whose habits are in the formative stage. Because a careful survey was conducted at the start, it should be possible to evaluate this program after a reasonable period. The success of this approach may well set the pattern for similar efforts in other cities.

The approach to the school child has to be realistic. The school boy or girl is more concerned about the effects of cigarette smoking on ability to participate effectively in sports, especially competitive sports, than the possible hazards of cancer in the vague and distant future. The cigarette is often regarded as a symbol of "growing up" and of being "one of the crowd". This point of view must be argued on an intelligent basis with the school child. The assistance of parents and teachers, and especially of the student leaders, is all-important if any program of health education is to succeed.

What about the medical profession? Why is their voice not heard? If the cigarette smoking habits of the population as a whole are to be influenced, the entire medical profession, not public health workers alone, must play a much more active role. If we really believe that cigarette smoking increases the likelihood of lung cancer, then why don't we say so through every ethical medium at our command? Better still, why don't we set an example by abandoning cigarette smoking in numbers which are bound to impress the lay public more than anything else we can say or do? If, in fact, many physicians have given up cigarette smoking or have altered their smoking habits, as we believe is the case, then why do we not obtain this information and announce the figures to the public as evidence of our belief in scientific facts?

We need not and should not ignore the role of air pollution over our cities. The increased atmospheric content of four polycyclic hydrocarbons in the air over urban areas and its relationship to the incidence of lung cancer has been pointed out by Stocks.[1, 2] Even more intriguing is the evidence that one of the four hydrocarbons, 3:4 benzopyrene which is also present in cigarette smoke and is a known carcinogen in laboratory animals, appears to be most closely related to mortality from lung

cancer. The medical profession should encourage programs designed to reduce this urban hazard.

There is an important job to be done in prevention of disease, and it is our responsibility to see that it is done. To quote from Prince Philip's presidential address to the Canadian Medical Association in 1959, "One thing I beg of you—don't go away from here saying 'This has got nothing to do with me and, anyhow, I'm fully occupied with curing disease', because you know it isn't true. You cannot afford to ignore the facts and still maintain that you are in the least bit interested in health."[3]

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THE MASSACHUSETTS GENERAL HOSPITAL: 1811-1961

> *"This hospital has always inspired the fervid attachment of those holding any relation to it whatsoever—whether as citizens, proud of its benevolent services; as pupils, grateful for its teachings; or as medical officers, who have put their own work into its comprehensive fields of usefulness. It has universally fostered a feeling of affection, such as is cherished for an Alma Mater."*
>
> —Oliver Wendell Holmes

FROM January 31 to February 2 this year a world-renowned institution, described on that occasion as "the eldest daughter of Harvard Medical School", celebrated its one hundred and fiftieth anniversary. The Massachusetts General Hospital is the oldest general hospital in New England and the third oldest in the United States.

Early in the nineteenth century the unhappy state of medicine in Boston, and indeed in all of the New World, stirred the compassionate soul of the Reverend John Bartlett, the chaplain of the Almshouse, as he met misery, anguish and hopelessness at every turn in his efforts to bring some small comfort to the inmates. On March 8, 1810, the Reverend Bartlett convened a meeting of the most eminent Boston citizens with the intent of founding a general hospital for the care of the physically and mentally ill. With the vigorous support and initiative of two of Boston's leading young doctors, James Jackson and John Collins Warren, a circular letter was forthwith despatched to the city's most influential citizens proposing that the necessary funds could be raised immediately "if a few opulent men will contribute only their superfluous income for one year". This letter, which has been called the cornerstone of the hospital, prompted an enthusiastic response and on February 25, 1811, the Massachusetts Legislature granted the charter for incorporation of the Massachusetts General Hospital. The first meeting of the corporation was held on April 23, 1811, with John Adams, ex-President of the United States, as moderator. The report of the legislative committee that recommended approval of the charter embodied the objectives defined in the Jackson-Warren letter and constituted a blueprint which has guided the course of this famous institution throughout its 150 years of service. As a "bill of rights for the sick in a free society", and the foundation of modern voluntary hospital systems, the contents of this report as reproduced in Joseph E. Garland's attractive booklet commemorating this anniversary occasion[1] are worthy of note.

The manner in which the M.G.H. has fulfilled the faith of its founding fathers is now a familiar matter of record, inscribed by a host of outstanding emissaries from every branch of the profession through their contribution to medicine in all of its multiple facets. The list of luminaries of the medical world who participated in the recent impressive scientific and ceremonial program of celebration bears witness to the esteem so justly commanded by the Massachusetts General Hospital as it embarks upon its one hundred and fifty-first year of service.

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THE INTERNATIONAL HIPPOCRATIC FOUNDATION OF COS

DURING the Tenth International Congress of Urology which was held in Athens and Cos in April 1955, a Hippocratic procession was organized at which the mayor of Cos, in his address to the participants, proposed the establishment of an International Medical Institute in Cos, in honour of the "father of medicine". Professor Spyridion N. Oeconomos of Athens, president of the Urological Congress, urged the delegates from 32 countries to support the creation of such an Institute. This plan received further approbation at the Third International Congress of Neo-Hippocratic Medicine at Montecatini in 1956.

In 1958 Professor Oeconomos issued an appeal to national governments, to UNESCO, and to medical organizations and physicians throughout the world requesting their support, assistance and cooperation. As a result of his vigorous promotional efforts, the government of Greece in October 1960 ratified by royal decree the statute of the International Hippocratic Foundation.

Current plans call for the erection of a central Hellenic pavilion with additional pavilions representing those nations participating in the project. The French Society of the History of Medicine plans to issue a special Hippocratic stamp, proceeds from the sale of which will be used for the erection

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of the French pavilion at Cos, and many other professional societies have pledged similar contributions. The Hellenic pavilion will house seven rooms on its ground floor, including a conference hall, library and dining room, with 20 bedrooms on the second floor.

A worldwide canvass of physicians for individual contributions is planned, and officials of the Foundation anticipate an enthusiastic response.

The International Hippocratic Foundation describes its objectives as follows: to disseminate and cultivate the ideal of medicine as conceived and practised by Hippocrates; to propagate the spirit of Hippocratic medicine with its central theme of dedicated service to mankind; to publish the writings of Hippocrates and other manuscripts concerning Hippocratic medicine; to stimulate the erection of hospitals, medical institutes and laboratories, both within the framework of the Foundation and independent of it; to provide doctors throughout the world, regardless of their sex, race or nationality, with an opportunity to spend some time in a peaceful environment where they may steep themselves in Hippocratic culture and medical, archeological or historical research in the Asclepeion and amidst the other archeological treasures of Cos.

Plans are being made to hold an International Medical Olympiad every five years at which views may be exchanged and various professional matters may be discussed. On this occasion an international committee will award a prize for the outstanding report on medical progress, the award to be presented to the recipient by the reigning sovereign of Greece.

By these means it is anticipated that the ancient medical school of Cos will be re-created as a component of an international medical centre.

To date 52 countries have appointed delegates to the Foundation. Canada's delegate is Dr. Sylvio Leblond of Chicoutimi, Quebec. W.G.

THE COMMON COLD

MUCH of the recent research on the subject of the common cold has been carried out in the fields of virus isolation and treatment.

Tyrrell and Bynoe[1] recently reported that they have now isolated a total of 25 cytopathic viruses from the nasal washings of patients suffering from typical common colds. Nine of these viruses produced colds in human volunteers, as did five washings from which no virus was recovered. They found that the individual volunteer's response and the average clinical picture produced by some strains were slightly different from those produced by others. These viruses also differ from each other in laboratory tests: they produce specific neutralizing antibodies, they attack different cells in tissue culture, and they have a "spectrum of cultivability" as shown by the ease with which they grow in either human and/or monkey-kidney cells.

The problem of the treatment of common colds with antibiotics has been investigated by McKerrow, Oldham and Thomson.[2] In this project two groups of subjects were studied: 138 ex-miners with pneumoconiosis and some degree of bronchitis, and 55 normal adults of both sexes. The trial had two objects: (1) to determine whether or not measures to subdue the severity of the common cold prevented exacerbations of bronchitis in those subjects with pneumoconiosis, and (2) to see if small doses of antibiotics taken at the beginning of a common cold can prevent secondary bacterial infection and therefore shorten the duration of symptoms in normal subjects. The criterion for success was taken as the disappearance of clinical manifestations of the cold after three days. "Active" and "placebo" lozenges were allocated at random to subjects in the trial. Great care was taken to achieve the "double-blind" principle. Results of this study indicate that recovery from common colds other than those starting in the chest can be speeded by treatment with antibiotics. This result was similar in both the bronchitic subjects and the normals. However, before the widespread use of antibiotics can be recommended for the treatment of common colds, extensive investigation on the development of drug-resistant organisms is needed. F.L.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

CREMATION

Cremation was the subject of a paper read at a recent meeting of the Winnipeg Medical Association by Dr. E. S. Moorehead. The figures presented by Dr. Moorehead show that, while cremation has not, as yet, impressed itself to any extent upon the public mind as a substitute for interment, there has been a steady increase in the number adopting this method. In England, the number in 1885 was three; in 1909, it was 855; in Germany, in 1908, there were 4050 cremations; and in such centres as Chicago and New York City, about one per cent of those dying in 1910 were disposed of in this manner. Some of the names taken from the lists of the English Cremation Society are the following: Grant Allen, Dr. Bernardo, Edna Lyall, Guy du Maurier, Sir Isaac Pitman, Lady Grey, Sir Spencer Wells, George Meredith, Sims Reeves, W. E. Lecky, Sir Henry Irving.

While many will agree with Dr. Moorehead that cremation is a "nicer, cleaner, and certainly more rapid means of disposal of human remains than is in vogue at the present day," earth-burial is so much a part and parcel of the custom and sentiment of the people that any wide change must be the matter of many years. And yet that is no reason why a change should not be advocated if it be proved that the present method is a dangerous one.—Excerpt from editorial, *Canadian Medical Association Journal*, 1: 458, May 1911.

LETTERS TO THE EDITOR

THE CONTROL OF PULMONARY VENTILATION

To the Editor:

In the March 4 issue (*Canad. M. A. J.*, 84: 471, 1961) there is a most interesting paper by J. C. Sinnott on this subject, in which he challenges, with a wealth of new experimental data on normal subjects and patients, the classical view of physiologists that CO_2 in the blood (pCO_2) is the all-important controlling factor for the respiration, by reason of the exquisite sensitivity of the respiratory centre to the tension of this gas in arterial blood. The classical view and its modification by others is excellently reviewed, and the data presented are of great value for testing any physiological theory. However, a case can be made that the interpretation of these data by Dr. Sinnott contains two logical fallacies.

His method is to plot the pCO_2 vs. the ventilation rate for specific subjects or patients, over a wide range of ventilation rates produced by various degrees of exercise, and to compare this with a plot of O_2 consumption vs. ventilation rate, for the same data (his Fig. 5). The correlation coefficient between the ventilation rate and O_2 consumption is high ($r=0.991$), but is much poorer between ventilation and $pACO_2$ ($r=0.236$, which is not significant). Dr. Sinnott suggests therefore that it is very difficult to accept the hypothesis that pCO_2 directly regulates the ventilation. On the other hand, he thinks that the respiratory centre responds in an orderly and predictable way to an increase in "work-stimulation" (evidently identified as measured by the O_2 consumption), regardless of the small and inconsistent change in pCO_2.

Exactly the opposite conclusion would appear to be the result of the usual thinking about control mechanisms, or homeostasis. The coefficient of correlation would seem to be quite irrelevant to the logic. It is the *slope* of the regression lines in the graphs, not the coefficient of correlation, that gives the clue to the nature of the controlled variable, and to the nature of the control. The fact that over such a wide range of ventilation rates, the pCO_2 remains statistically constant or changes very slightly, is indeed the indication that this is the controlled variable of the homeostatic mechanism, and the simplest hypothesis is that fluctuations from the controlled value of pCO_2 of blood reaching the centre are the direct stimulus to the homeostatic adjustments of the ventilatory rate. The more sensitive the regulation (and he admits, the ventilatory rate has been shown to be most remarkably sensitive, at least to changes of inspired pCO_2), the more difficult it will be to obtain a significant correlation coefficient without measurements of arterial pCO_2 that are of very great accuracy. The sensitivity of the normal respiratory centre to an increase of arterial pCO_2 may be so great that very accurate measurements, far more accurate than would appear from the scatter of points in Fig. 5 of Dr. Sinnott's paper, would be required to obtain the correlation. It is the very constancy of pCO_2 over the wide range of ventilation rates in exercise that is the strong evidence that this is the "controlled variable" of the system. The simplest and most direct way to control a variable in a homeostatic system is to have its own fluctuations actuate a "negative feedback" system. Yet in the paper, Dr. Sinnott cites the constancy of pCO_2 as evidence *against* the classical theory!

A simple analogy may make the contrary view plain. Suppose that the temperature of a room is controlled by a thermostat, in the room, which turns up or down a heater. The more effective the control system is, the less likely it is that one could show any significant correlation coefficient between the temperature of the room and the output of the heater, throughout the varying climatic temperatures of a winter. Would Dr. Sinnott conclude, from failure to show such a correlation, that the temperature of the room was not controlling the heating system?

There is of course in control systems a "load error". The controlled variable, here the pCO_2, cannot remain absolutely constant as between rest and heavy exercise where the sustained ventilation rate is much greater. A rise in the maintained level of pCO_2 is required to give the sustained stimulus for the increased ventilation, but this rise may be very slight and below the errors of measurement of arterial pCO_2. Such a correlation, i.e. in load error, was shown in the classical researches between ventilatory rate and the alveolar pCO_2. It is thus possible to conclude from the data exactly the opposite of what Dr. Sinnott deduces from them.

The second logical fallacy is concerned with what Dr. Sinnott calls the "oxygen-ventilation equivalent" (VO_2), which is the ratio of the total ventilation to the oxygen consumption. He states: "It is an exact measurement of the respiratory response per unit of oxygen consumed, and although it does not quantitate the activity of the respiratory centre in absolute terms, it is at least an accurate index of the activity during muscular exercise."

Now this ratio enjoyed a brief popularity some 20 years ago, during wartime research in pulmonary function. At that time it, or rather its reciprocal, was called the "efficiency of breathing" and it was thought by some that the ratio must reflect the ease with which O_2 was absorbed in the lungs. However, I made the discovery at that time that, on the contrary, this ratio depended on the maintained level of pCO_2 and little else. Though this was not published at the time, the relation is now well recognized, and is explained in textbooks. For example, in his article in Ruch and Fulton's "Medical Physiology and Biophysics" (W. B. Saunders Company, Philadelphia, 1960, p. 807), Loren D. Carlson explains the relation, and says of it: "In order to maintain a normal alveolar CO_2 (and hence a normal arterial blood CO_2) the ventilation must be 16 times as large as the oxygen consumption at all levels of activity. *Any deviation from this simple relation signifies an alteration of alveolar CO_2.*" I would want to add "or in respiratory quotient".

The proof is very simple, and is based on changing from O_2 consumption to CO_2 production, by introducing the respiratory quotient R.

$$R = \frac{\dot{V}_{CO_2}}{\dot{V}O_2}$$

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Then

$$(O_2V) = \frac{\dot{V}_{BTPS}}{\dot{V}O_2} \quad \frac{\dot{V}_{BTPS}}{\dot{V}CO_2} \times R$$

Now since no appreciable amount of CO_2 is inspired, $\dot{V}CO_2/\dot{V}_{BTPS}$ must equal the fraction of CO_2 in the expired air, F_{CO_2E}.

i.e. $$(O_2V) = \frac{R}{F_{CO_2E}} = \frac{R \times P_B}{P_{CO_2E}}$$

where P_B is the total pressure. If changes in respiratory quotient are not involved, and in the steady state these are likely to be minor in rest vs. exercise, there is an inescapable inverse relation between this rather mysterious "oxygen-ventilation equivalent" and the pressure of CO_2 in expired air. The relation between the latter and the alveolar pCO_2 tension is well known, and involves only the volume of the dead space relative to the minute volume (about 1/3 to 1/4). This also proves to be a remarkably constant relation during exercise. We see then that there is an inescapable, logical, mathematic connection between the "oxygen-ventilation equivalent", which Dr. Sinnott wishes to place in the fundamental importance in respiratory control, and the arterial pCO_2 which it would replace in that role. Fig. 9 of Sinnott's paper shows how remarkably this prediction of the inverse relation applies to his data, including both normals and patients. He chooses to plot the data, in Fig. 10, by a semi-logarithmic relation, but actually the curve of Fig. 9 is the hyperbola predicted above. His (O_2V) is reciprocally related to P_{ACO_2}.

It follows that any argument Dr. Sinnott uses as to the fundamental importance in respiratory control of his (O_2V) applies equally well to the arterial pCO_2 of classical theory! It will be impossible, on his data alone, to decide which of the two quantities is cause, and which effect. To do so we would have to concentrate on cases where the mathematical relation deviated, because of changes in respiratory quotient, and in relative volume of dead space. The issue must be decided on other grounds than these correlations.

I find it impossible to conceive how the respiratory centre can be directly affected, or "sense" the oxygen-ventilation equivalent, or the oxygen consumption of the whole body, except through changes in arterial pO_2. The sensitivity of the centre to pO_2 has been shown to be quite inadequate to explain the control of respiration by the centre. On the other hand, the response to pCO_2 has been proved to be of a most remarkable sensitivity. Dr. Sinnott's data therefore confirm my belief in the classical theory.

The importance of the main point made by Dr. Sinnott is not denied. Undoubtedly factors other than the level of arterial pCO_2 control the respiration in exercise, as the papers cited in his excellent review of the classical literature have shown. In disease states also, other factors must be considered. His point in the introductory paragraphs, that the classical work on the respiratory response to artificially increased alveolar pCO_2 does not necessarily prove the classical control by CO_2 in physiological states, as in exercise, is also valid.

What this letter intends is merely to point out that his excellent new data do not necessarily disprove the classical theory of respiratory control, but are entirely consistent with that theory in terms of "negative feedback" control. The second point is that in his "oxygen-ventilation ratio", which he feels is an index of the "respiratory drive" and "activity of the respiratory centre", he has, not an independent measure of anything, but something that is mainly dependent on the pCO_2. Any evidence that the oxygen-ventilation ratio is important, applies also to the pCO_2.

It is indeed intriguing that the same impressive set of physiological data lends itself to such opposite conclusions in the minds of different physiologists. It is this feature which makes physiology such fun for its devotees, and stimulates them to enjoyable controversy.

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To the Editor:

There are no "logical fallacies" in the thesis to which Professor Burton refers. His conclusion in regard to Fig. 5 would be correct if one assumes a continuously changing sensitivity of the respiratory centre to pCO_2. His second objection is not acceptable either. Even if Figs. 9 and 10 were incorrect, which they are not, the mistake would be a slightly different interpretation, not a "logical fallacy". It seemed to me unnecessary to detail my theoretical approach to the problem of assessing the adequacy of the classical theory. However, an outline of some logical reasoning in this regard is evidently required.

It has been known for fifty years that there is a direct linear relationship between an increase in pCO_2 and pulmonary ventilation in resting subjects. This observation proves that CO_2 is a respiratory stimulant (within limits); but that is all that it proves. It was also established that the pCO_2 did *not* increase during exercise despite the much greater respiratory response attainable; and recently it has been shown that pCO_2 will even decrease in strenuous exercise. Stated another way: the motor discharge of the respiratory centre may be much greater during exercise with *no change* (or even a decrease) in pCO_2 but an *increase* in pCO_2 in resting subjects is required for it to deliver even a lesser output. Obviously, the respiratory centre is behaving differently during exercise if one assumes pCO_2 to be the regulator. Therefore, if one accepts the classical theory, one is forced to postulate some intermediate factor or factors in order to resolve this discrepancy. The usual approach, to which Professor Burton subscribes by implication, is to invoke the "changing sensitivity" hypothesis, which is necessary if a "feed-back" control is operative. This postulate requires that there be an immediate alternation in the sensitivity of the respiratory centre to pCO_2 with each increment of exercise. Serious consideration of this postulate suggests the next logical question: What causes the delicate change, and by what mechanism is it effected? It cannot be the pCO_2, because it did not dictate that it remain constant in the resting state. It must be something else. This line of reasoning leads, therefore, to one more postulate, perhaps two, in order to explain the operation of the first; so that we will have at least two, perhaps three, hypotheses, each dependent upon the validity of the others in order to explain the discrepancy. It is an axiom of scientific investigation that only the minimum number of hypotheses should be advanced to explain a given phe-

nomenon. On this basis alone, the hypothesis is not well founded. Moreover, the experimental data of the past forty years do not support it.

One cannot refute the reasoning outlined above by invoking a "feed-back" mechanism, because the same arguments apply. In this respect, the analogy with thermostatic control of room temperature is not apt because the heater will work at full output until the temperature (analogous with pCO_2) comes back to the original setting. The heater does not respond at a lesser output to allow the temperature to remain at a different level, as happens with pCO_2 in resting subjects. Discussions of "feed-back" controls and mechanical analogies usually confuse the issue. A "feed-back" control or changing sensitivity might be operative; but this possibility was investigated and rejected, as was shown clearly in the thesis.

It was with the considerations outlined above that this investigation was undertaken. Insofar as pCO_2 is concerned, we begin with three established facts:

1. Ventilation increases linearly up to 70 litres per minute with increases in pCO_2 from 40 to 60 mm. Hg.
2. pCO_2 remains constant during muscular exercise.
3. We find that pulmonary ventilation increases linearly with increases in the work stimulus.

Some of the data were illustrated in Fig. 5 in a normal subject, and in Fig. 7 in an abnormal subject, in order to demonstrate that points (2) and (3) (above) are correct and to emphasize the difference in "behaviour" of the classical stimulus (pCO_2) between rest and exercise. In view of the *increase* in pCO_2 required to increase ventilation at rest (i.e. (1) above), it is certainly "difficult to accept the hypothesis that the [constant] pCO_2 directly regulates these rather precise exercise stimulus–response curves". It is obvious that Fig. 5 cannot by itself disprove the adequacy of the classical stimulus. However, Fig. 5 does make that adequacy doubtful, and it suggests the necessity for some further investigation.

In view of the results shown in Fig. 5, two possibilities now exist in respect of pCO_2: (1) either pCO_2 is not the regulator of the exercise curve of work and ventilation, or (2) the respiratory centre becomes progressively more sensitive to pCO_2 during increasing exercise by means of some undetermined mechanism. The latter hypothesis, discussed above, seemed unlikely, but the possibility still required exploration. This was done; and Figs. 11, 12, 13, 15 and 16 disprove it completely. I find it impossible to understand how Figs. 11, 12, 13, 15 and 16 would help confirm Professor Burton's belief in the classical stimulus.

Some further consideration is, it seems, necessary in regard to my use of the oxygen ventilation equivalent (O_2V). The O_2V is merely a mathematical expression of the slope of the exercise stimulus–response curve. As such, it is certainly an index of the sensitivity of the respiratory centre to changes in the work stimulus. Moreover, it *may* be used, if one wishes, to express the activity of the respiratory centre in relation to a given work stimulus. It is illogical to state that I "would replace pCO_2 with O_2V in the primary role in respiratory control". The O_2V is only ratio; it cannot replace anything, nor could it cause anything. The O_2V was used only as a measurement to assess the adequacy of the classical primary stimulus, not to replace it. A voltmeter which measures the output of a generator gives no clue to the type of engine being used to drive the generator; it does however indicate the adequacy of the voltage regulator. Similarly, the O_2V cannot be expected to "stimulate" the respiratory centre or to identify the forces driving it. How could the respiratory centre "sense the O_2V", which is a product of it? Secondly, how could the O_2V be dependent upon pCO_2? If the sensitivity of the respiratory centre to the stimulus of exercise was found to be increased (high O_2V), as it was in many of my patients, the pCO_2 will then be low. To state that the O_2V is dependent upon the pCO_2 is to insist that a low pCO_2 causes hyperventilation, a conclusion which is ridiculous. Certainly, there is a logical mathematical relationship between pCO_2 and O_2V because both are determined by the respiratory centre. The pCO_2 is inversely related to the O_2V, but the values of both depend upon whatever factors are driving the respiratory centre. Neither regulates the centre; both are products of it. If those considerations are kept in mind, confusion of stimuli and methods of measurement will be avoided.

Professor Burton's objection to Figs. 9 and 10 has no bearing on the problem of respiratory control. The relationship shown is inverse, which is the important thing. Professor Burton would prefer to relate O_2V to the expired CO_2. Such a relationship must exist; but this is a tangential issue which serves only to obscure the real problem, which is the assessment of the adequacy of arterial pCO_2. The discussion of pCO_2 and O_2V above clarifies the reasons for a necessary relationship. Nevertheless, an attempt was made to plot the data of those 750 experiments, shown in Fig. 9, as a reciprocal curve, because of the obvious relationship referred to by Professor Burton. However, the correlation was not as significant as that of the exponential curve. Accuracy, therefore, dictated that the exponential curve be used rather than the rectangular hyperbola. Although the question has no relation to the problem of respiratory control, one may speculate on the reasons for this; and the following are probably partially responsible: the dead-space did not bear a constant relationship to the tidal volume, the expiratory exchange ratio varied between different experiments, and the dead-space of those patients who hyperventilate was less than that of the normal subjects.

Professor Burton states, "It will be impossible, on his data alone, to decide which of the two quantities (i.e., O_2V and pCO_2) is cause and which effect." The resolution of this difficulty, if there is one, is simple: both are effects of the respiratory centre. The O_2V is certainly an effect, as was shown above; that is why it was used as a measuring device to quantitate the activity of the respiratory centre. The pCO_2 is also an effect, as the data show clearly.

Everybody, including Professor Burton, seems to recognize an "exercise factor" in the control of pulmonary ventilation. Those who insist upon the primacy of pCO_2 usually ignore it, because it has not been possible to reconcile it with the classical theory. However, there seems little doubt that some remarkably precise mechanism(s), quite different from the classical stimuli, is (are) acting upon the respiratory centre during exercise. To ignore them contributes nothing to the solution of the problem of control of the respiratory centre. In this respect, Professor Burton would avoid discussion of Figs. 11, 12, 13, 15, 16 and 17; but he still wishes to interpret the data as consistent with a "negative feed-back" control. The data illustrated in those figures clearly make that impossible. His criticism of my conclusions regarding the adequacy of the classi-

cal theory are invalid, because they presume the validity of the classical theory. Similarly, belief in the classical theory and a simple mathematical relationship should not mislead one to the conclusion that hyperventilation (high O_2V) is dependent upon a low pCO_2 (second last paragraph of Professor Burton's letter). It seems obvious to me that a low pCO_2 cannot be the cause of hyperventilation.

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MEDICAL NEWS IN BRIEF

CIRCULATORY EFFECTS OF PIPE AND CIGAR SMOKING

Much attention has been devoted to the effect of smoking cigarettes on the circulation but relatively little information is available on the circulatory action of pipe and cigar smoking. Such information seems important because of the large amount of tobacco consumed in these forms.

In a study by Simon and Iglauer (*Am. J. M. Sc.*, 241: 22, 1961) ballistocardiograms, blood pressure, pulse rates and skin temperatures were studied in volunteer cigar and pipe smokers during and after smoking. The usual effects of tobacco smoking on the circulation were found (i.e. increase in pulse and blood pressure, drop in skin temperature), but were not as marked as those found following cigarette smoking or chewing tobacco. The incidence of changes in the ballistocardiograms in this study was less than that found following chewing tobacco, but greater than that found following cigarette smoking. The circulatory effects of cigar and pipe smoking were approximately the same. Circulatory changes were slightly less following low nicotine cigars and pipes when compared to standard cigars and pipes. Sham smoking did not produce circulatory changes.

This study indicates that failure to inhale does not prevent appearance of the usual circulatory effects of nicotine. Very few previous studies of pipe and cigar smoking were found.

MORTALITY IN RELATION TO SMOKING HABITS IN CANADA

A rising death rate from lung cancer has been reported in many parts of the world and numerous studies have been made of the factors associated with this increase. Research has been directed toward four general aspects of the etiology of lung cancer: epidemiological and statistical, pathological, chemical and experimental. Epidemiological and statistical studies have shown a definite association between cigarette smoking and lung cancer and this finding has been supported by data from the other types of studies.

A Canadian study which began in 1955 has recently been reported in preliminary form by Best, Josie and Walker of the Department of National Health and Welfare (*Canad. J. Pub. Health*, 52: 99, 1961). Previously, attention has been called to the rapid rise in the lung cancer death rate in Canada from 1931 to 1952. The age standardized death rate due to primary and secondary lung cancer increased from 2.4 to 10.7 per 100,000 poulation. For males this rate increased from 3.0 to 17.0; and for females, from 1.6 to 3.7. In the same period the proportion of lung cancer deaths to all deaths due to cancer rose from 2.2 to 8.7%.

In 1954 the Department of National Health and Welfare began a prospective study in the form of a questionnaire survey to investigate the relationship of smoking, and the possible relationship of other factors such as residence and occupation, to lung cancer.

In reviewing the preliminary statistics from this survey, the consistent relationship between cigarette smoking and excess total mortality stood out clearly. These data indicate that mortality increases with the intensity of cigarette smoking reported. Discontinuing cigarette smoking apparently reduces the death rate. For cigar and pipe smoking, there is little overall evidence of any excessive mortality as compared to non-smokers. An association was also evident between cigarette smoking and elevated death rates for arteriosclerotic heart disease and lung cancer. In general the findings in this study with regard to the relationships between mortality and smoking habits, particularly cigarette smoking, are consistent with those of other prospective studies.

SURVIVAL OF PATIENTS WITH CANCER OF LARGE INTESTINE AND RECTUM

A detailed 15-year survival analysis by stage, age, calendar period of diagnosis and type of treatment for 7128 patients with cancer of the large intestine and 5082 patients with cancer of the rectum diagnosed in the State of Connecticut between 1935 and 1954 is presented by Ederer, Cutler, Eisenberg and Keogh (*J. Nat. Cancer Inst.*, 26: 489, 1961). These data describe the experience of virtually all patients with these diseases in a community, rather than that of patients admitted to an individual hospital or treatment centre. Observed survival was measured relative to expected survival in the general population. For cancer of the large intestine and rectum, five-year survivors experienced considerably higher mortality than persons of similar age in the general population. Ten-year survivors experienced approximately normal survival between the 10th and 15th years after diagnosis. Five-year relative survival rates improved dramatically from 1935-44 to the post-World War II period 1945-54 (large intestine: males, 19 to 32%; females, 23 to 39%; rectum: males 15 to 30%; females, 23 to 32%). Improvement was noted for patients with localized disease and with regional spread. The relative number of untreated patients decreased from 1 in 4 to 1 in 6 for cancer of the large intestine, and from 1 in 5 to 1 in 7 for cancer of the rectum. More frequent operation and increase in length of survival of surgically treated patients contributed to the overall improvement. Most of the increase in the five-year relative survival rate for surgically treated patients resulted from an increase in the one-year survival rate which suggested that reduction of operative mortality was an important factor.

The outlook for women tended to be more favourable than for men, but this sex difference was not evident in the case of carcinoma of the rectum during the second period of diagnosis, 1945-54.

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MEDICAL MEETINGS

CONFERENCE ON EMERGENCY HOSPITAL SERVICES

A conference to discuss ways and means of providing emergency hospital services in time of national disaster was held at the Canadian Civil Defence College, Arnprior, Ontario, on March 27, 28 and 29, 1961. Approximately 80 persons, including hospital administrators, physicians, nurses and others, attended this conference, which was convened jointly by the Department of National Health and Welfare and the Canadian Hospital Association.

The objects of the conference were to bring the participants up to date on current government planning in regard to attack by nuclear weapons and to have them provide the government with advice on establishing emergency hospital services for use during such disaster. Five basic questions were posed: How should emergency hospital services be established outside target areas? Where should emergency stockpiles of medical supplies be pre-positioned? Should additional auxiliary hospital personnel be trained in advance? Are available educational pamphlets and courses on emergency health services adequate? Is additional legislation necessary to fulfil Canada's needs for these services?

Many thousands of people would be killed by a nuclear explosion on a target city, either from the explosion itself or from exposure to radioactive fallout. The objective of emergency planning of hospital services is to save as many of the survivors as possible, by utilizing hospitals in cities, towns and villages outside target cities.

It was the conclusion of the conference that hospitals in the outlying areas of large cities which are likely to be targets, should be prepared to expand their local services and, as well, provide the framework for the operation of emergency hospitals or improvised hospitals in their areas. The flow of casualties would be from the target city to hospitals in the periphery. In some areas, the shortage of medical and hospital personnel may make it necessary for a number of smaller hospitals to group together in planning emergency hospitals in their areas.

The location of improvised hospitals, as well as the allocation of medical, nursing, and auxiliary personnel to these various sites, would be the responsibility of provincial or local emergency health service authorities.

The Conference was advised that the Federal Government now has a number of complete treatment centres, and improvised hospitals, as well as stockpiles of bulk medical supplies and equipment which will be pre-positioned at hospitals and other emergency locations outside target areas. These supplies will then be available in time of emergency. Drugs and other supplies which have a short shelf-life will have to be replaced from time to time, and utilized by active treatment hospitals, when their half-life period is reached. This would be arranged by Federal or Provincial authorities. The Conference suggested that the Federal Government might give financial assistance to those hospitals which have to build or rent storage space for emergency supplies.

National Health and Welfare

C.M.A. representatives attending the conference are shown with Dr. A. C. Hardman, Chief of Emergency Health Services, Department of National Health and Welfare. Left to right: Dr. A. F. W. Peart, Dr. Nathan Levinne, Dr. Burdett McNeel, Dr. Hardman and Dr. W. I. Taylor.

It was agreed that various auxiliary hospital personnel would be needed in great numbers in time of emergency, and hospitals are encouraged to organize and train as many auxiliary workers as possible in their areas. It was also suggested that all high school students should receive some training in emergency hos-

National Health and Welfare

Councillors and surveyors of the Canadian Council on Hospital Accreditation who attended the conference included (left to right): Dr. W. I. Taylor, Dr. Douglas Piercey, Dr. Burdett McNeel, Dr. Nathan Levinne, Dr. Arnold Swanson, Dr. L. O. Bradley and Dr. Paul Laplante.

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National Health and Welfare

Dr. G. E. Fryer, Miss L. H. Parsons (Oakville, Ont.), Father H. F. Bertrand and Dr. N. Levinne are examining equipment displayed at the conference.

pital and medical services, such as first-aid or auxiliary hospital training, as well as in the fundamentals of survival. This would provide a ready source of supply of auxiliary personnel in time of emergency.

It was also recommended that the available literature on emergency planning, although it is fairly adequate, be more widely distributed; additional literature on specific types of training would be desirable. General publicity concerning the need for emergency planning should be stepped up for all segments of the public, but particularly for hospital and medical personnel. Institutes for health personnel should be continued at Arnprior but should be encouraged at the provincial level, where local interest might be engendered.

Participants at the conference felt that persons in charge of emergency hospital services, locally and provincially, should be given some measure of legal authority to direct people in time of emergency.

A. F. W. PEART

INTERNATIONAL CONFERENCE ON BIOLOGICAL ASPECTS OF SCHIZOPHRENIA

At a three-day International Conference on the Biological Aspects of Schizophrenia, held in New York, April 6-8, 1961, under the sponsorship of the New York Academy of Sciences, research findings in mental illness were presented by more than 100 leading investigators.

Emphasizing the molecular basis of mental processes, Fuller of the Roscoe B. Jackson Memorial Laboratory in Bar Harbor (Maine) suggested that temporary chemical imbalances during early life and basic perceptual learning stages may cause damaging changes in behaviour patterns.

Many of the papers read at the conference dealt with the roles of neurohormones such as noradrenaline, catecholamines and serotonin, and the effects of psychotomimetic drugs in mental behaviour.

Serotonin, the potent adrenaline-like substance produced by the body and which is regarded as a major factor in mental functions, was reported to be depleted under the influence of a tranquillizer such as reserpine, while release of noradrenaline or other brain catecholamines does not take place. When, however, reserpine is given after pretreatment with a monoamine oxidase (MAO) inhibitor which blocks the release of serotonin, it produces excitation rather than tranquillization by causing the release of catecholamines rather than serotonin.

Sankar of Creedmoor State Hospital, New York, and Chairman of the Conference, described tracer work demonstrating that ISD, the hallucinogenic drug used to induce psychosis for experimental purposes, produces an increase in free serotonin in brain tissues while the tranquillizer, chlorpromazine, causes a decrease in brain serotonin.

Several authorities reported evidence of the existence of a factor in the blood of schizophrenic patients which, when injected into experimental animals, alters their responses and general behaviour. The factor itself has not as yet been isolated or identified. Sankar reported that serotonin uptake by the blood platelets of schizophrenic children is lower than in normal children, while inorganic phosphates are present in plasma and erythrocytes in higher amounts in the schizophrenics. The latter, he believes, may result from some disturbance in cellular energizing mechanisms centred around adenosine triphosphate (ATP).

Freedman (Yale University School of Medicine) told the conference that LSD affects the level of serotonin in the brain. He suggested that the autonomic and mental effects of serotonin may depend not only on its levels within cells but also on the status of the substance—that is, whether it is bound or free. Freedman also emphasized that the problems are far from resolved. In determining the etiology and therapy of mental disorders – schizophrenia in particular – three factors must be borne in mind at all times: the psychosocial, the learning experience, and the neurochemical. Moreover, the last may be subdivided into biochemical and neurophysiological.

One of the difficulties of studying schizophrenia is the major problem of designing valid experiments and in correlating the data obtained—to establish the connection between experimental model psychoses and clinical schizophrenia. Woolley of the Rockefeller Institute, who first proposed the theory of disturbed serotonin metabolism in schizophrenia (1954), acknowledged these difficulties but emphasized that the major evidence confirms the depressant effect of a depletion of brain serotonin, and the excitatory effects resulting from an excess.

Changes in the brain levels of serotonin are now reasonably well established. Woolley believes that the next step is to study serotonin in cellular structures, rather than from gross brain homogenates, since serotonin disturbances probably operate in localized cerebral regions.

Further complications in the problem of evaluating data arise from the fact that drugs that influence physi-

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VIEWS ON THE ECONOMICS OF MEDICINE

Prepared by the Department of Medical Economics. The Canadian Medical Association

MAY 6, 1961, NUMBER 17

Our sources of information are private communications and published comments in medical journals and the lay press. These are usually reliable but incorrect quotation or interpretation is always possible.

The following extracts from the radio address of the Honourable J. Waldo Monteith, Minister of National Health and Welfare, presented in the series The Nation's Business on April 7, 1961, are reproduced for the information of the medical profession. They may be regarded as expressing the attitude of the government of Canada to current projects in health and welfare, and, in the absence of more detailed information on the Royal Commission on Health Services, they will serve to set the stage for the studies which that body will undertake.

"Someone has said that the most powerful thing in the world is an idea when its time has come. One idea that has come into its own in our era is social justice. We have only to look at news reports from any part of the globe to realize what a tremendous impact this concept is exerting on twentieth century life.

"The Prime Minister has called social justice 'the concept of fairness to each and fairness to all'. Thinking in terms of health and welfare, this implies a number of things. It means that every Canadian should have access to the best health care available. It means that Canadians in their declining years should enjoy an adequate measure of economic security. It means that Canadians in their working years should be protected against various social and economic hazards of modern industrial society. It means that the coming generation should have opportunities for development which will enable them to meet the challenges of our country's future.

"These aspects of social justice are easy enough to put into words. They are not quite as simple to put into practice. None of them can be achieved overnight. The road to social justice is a gradual development, not a hundred-yard dash. Moreover, in our free and democratic society, they cannot be achieved by government action alone. They can only come about through the concerted effort of government, industry, labour, voluntary agencies, professional groups, and individual Canadians themselves.

"Old age pensions have been raised to the highest level in their history. The same applies to pensions for the blind and for the physically disabled. Residence requirements for old age pensions have been cut in half. Recipients of Old Age Security have been granted the right to take their pensions with them when they leave Canada either temporarily or to live abroad permanently. The only requirement for permanent absence is that a pensioner should have resided in Canada for twenty-five years after his twenty-first birthday.

"Federal financial support of Unemployment Assistance benefits has been greatly expanded. Among other things, this has enabled many provinces and municipalities to give additional aid to old age and other pensioners who are in particular need. Incidentally, the Dominion Government places no ceiling on the amounts which we will share under this program. We will pay half of whatever the provinces and municipalities see fit to grant needy pensioners in terms of added benefits other than medical care.

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"We have also undertaken a long-term study of the whole structure of Canada's pension programs. Some people feel that we are taking too long with this study. They accuse us of delaying tactics. My answer would be to remind them of one sober fact. In the current fiscal year, the federal Treasury will be spending over $600 million on old age pensions alone. This is close to half of my department's total budget. We are anxious that before any steps are initiated to increase this amount—either through improvements in present programs or through the addition of a contributory scheme—we should have a full and accurate assessment of what is involved.

"In the field of health, I would refer to the Hospital Insurance and Diagnostic Services plan which is now in effect in all ten provinces and the two northern territories. Under this scheme, more than $370 million in federal funds have been paid to the provinces and territories, which is altogether new money as far as they are concerned.

"We have more than doubled federal grants for hospital construction and have extended this assistance to include renovation of existing hospital facilities and the building of internes' residences. Assistance has been increased in other fields such as mental health, medical rehabilitation, professional training and public health research. Increased attention has been given to the matter of fitness and recreation and the Government is presently considering positive steps by which our youth can be encouraged to take part in amateur athletics.

"Finally, last December, Prime Minister Diefenbaker made an announcement in Parliament which may well prove to be one of the major turning points in the history of Canada's health progress. He indicated, as you may recall, that a Royal Commission would be set up to make a comprehensive study of Canada's national health requirements and the existing deficiencies in health care with a view to considering the establishment of a national health plan. This Commission is to be headed by a distinguished Canadian jurist, the Hon. Emmett Hall, Chief Justice of Saskatchewan. I would like to explain the Government's thinking in appointing a Royal Commission at this stage.

"As in the case of Old Age pensions, the first point to consider is the financial stake involved. This is very considerable indeed. In 1958—the latest year for which firm figures are available—Canada's total bill for personal health care was estimated at almost $1.2 billion. It you analyze this tremendous outlay, you will find that slightly more than half went for hospital care, possibly a third for payments to physicians and dentists, roughly 9% for prescribed drugs, and the remainder for other health services such as private duty nursing.

"The first segment of this national health bill—hospital care—has, of course, already been placed to a large degree on a public basis through the Hospital, Insurance and Diagnostic Services program and other arrangements. The fact is, too, that costs of hospital care have been rising constantly for many years—long before the insurance program came into being. These increases will probably continue but they may tend to slow down as earnings of hospital personnel reach levels comparable to those in other walks of life. Nevertheless, in planning for the future, this rather worrying situation has to be taken into account.

"What about the second half of our national health bill—the payments we make for the services of physicians, dentists, drugs, and other health services? This, of course, is the real question at stake today. It is the area with which the new Royal Commission will be particularly concerned. Besides its financial implications—which in 1958 involved something over $600 million—this area poses other far-reaching considerations.

"There is, for example, the problem of complexity. Hospital care, for its part, is relatively tangible and concrete in that it is centred in institutions where costs and services can be clearly defined. And yet even here, we faced substantial difficulties in putting it on a public basis. We had to solve such problems as preserving provincial jurisdiction and responsibility for administration, maintaining the autonomy of hospitals and ensuring a basic uniformity of services of high quality for all Canadians.

"These problems were, however, relatively simple in comparison with those to be faced in tackling a program of medical care. In this instance, we are not dealing solely with specific entities like hospitals but with a whole host of varied circumstances. Over and above all this, are such difficult questions as how under a public program do you ensure that patients are free to consult the doctor of their own choice? How do you ensure that a good doctor enjoys an income in keeping with his abilities? And how, furthermore, can these things be done in a setting which allows the doctor freedom to exercise his own judgment with the interest of his patients as the sole consideration? Or to put it another way: how do you avoid bureaucratic interference with the actual practice of medicine? It is this kind of thing that contributes a degree of complexity to the subject of medical care which is largely absent from the hospital field.

"There is another aspect of importance. By the time hospital insurance was introduced on a public basis, it had, by and large, been accepted in principle by the people of Canada. It was no longer a matter of real controversy. This is not the case with medical care. Here is a subject about which there is still a wide divergence of opinion. Many groups are strongly in favour; others are almost equally opposed. Perhaps greater knowledge and understanding will narrow this gap. In any event, the Royal Commission will be much concerned with this angle and will be considering and weighing viewpoints from all quarters.

"Having in mind the various factors I have mentioned—the tremendous financial stake involved, the complexity of the problem and its controversial nature—I think it should be apparent why the Government has felt it wise to place this matter in the hands of a Royal Commission at this stage.

"But I want to make one point abundantly clear. The Government is keenly aware that further steps must be taken if Canadians are to achieve social justice in the realm of health care. Our thought is simply that when such steps are taken, they should be taken wisely and in the best interests of the nation as a whole. What we are after is a program that will meet the needs of our people and that will also enjoy the wholehearted support and backing of those professional and other groups who are involved in ministering to these needs. We are confident that the new Royal Commission will make a major contribution to this end."

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CANADA FACES DOCTOR SHORTAGE

(Quoted from Toronto Globe and Mail, April 6, 1961)

"The Canadian medical profession, after a searching self-examination, is showing symptoms of anxiety.

"Almost the entire current issue of the Canadian Medical Association Journal and a large part of the forthcoming issue of the Ontario Medical Review, are concerned with an introversive analysis of medical education in Canada.

"The precipitating cause of this mass contemplation of the medical navel is a growing realization that Canada is faced with an inadequate supply of doctors—many of whom may be of only borderline ability—at a time when an increased supply of first-rate men is essential.

"'At no time since the Flexner report of 1910,' says Dr. J. A. L. Gilbert, associate professor of medicine, University of Alberta, 'has medical education been under closer scrutiny than it is today.'

"'It is useless,' says Dr. J. E. F. Hastings, associate professor of public health and preventive medicine, School of Hygiene, University of Toronto, 'to snip off a piece from the curriculum here and add a piece there. The whole basis of medical education must be rethought so that it will produce in the future the kind of physician who is able to meet the challenge of changing patterns.'

"The seriousness of the imminent shortage of doctors is indicated by studies made by the Association of Canadian Medical Colleges. The ACMC studies show there has been a steady drop in registration in each year of the medical course in Canada during the three years 1957-1960, except for the fourth-year group in one year.

"They also show that there will be no increase in the number of medical graduates for the next three years at least, and that 'too many students of low academic potential are being registered, and not enough brilliant ones.'

"Dr. J. S. Thompson, secretary of ACMA, also points out that 35 per cent of the newly registered doctors in Canada are foreign-trained, yet Canadian medical schools could have enrolled 78 more first-year students without changing existing medical school facilities.

"Dr. MacFarlane, in the Ontario Medical Review, says: 'With the expected increase in population, it is wholly unlikely that we shall be able as in the past few years, to depend on immigration to maintain a favorable population ratio.

"'It is difficult to estimate the numbers of immigrant doctors in the next ten years, but excluding the possibility of any increased supply from that source, there will need to be approximately 300 new places in Canadian medical schools by 1970 to maintain the present physician-population ratio. Even allowing for the filling of half the needs by immigration, there will still remain a need for 150 new places.'

"The present physician-population ratio is not entirely adequate across the country. The over-all ratio in 1959 was one to 918.

"The doctors feel that three major difficulties stand in their way: the high cost of medical education, the long training period required, and the drop in prestige doctors have suffered over the years."

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ology may also be subject to a chemical change that converts them into more active or less active substances. This effect, together with other pharmacological variables, must be considered in measurements of blood levels of the psychoactive drugs, according to Carr of the National Institutes of Health. Carr explained that blood levels alone cannot be regarded as reliable indices to therapeutic responses because of the complex metabolic changes that drugs undergo. Also, blood levels may not represent equilibrium in tissues, and consistently high blood levels are not always indicative of optimum therapeusis.

The critical role of drug metabolites in drug action is exemplified by imipramine, an iminodibenzyl derivative with a molecular structure similar to chlorpromazine. According to Sulser, imipramine may act as an energizer. The change in mechanism appears to be attributable to the metabolite that forms in the body—monomethyl nor-imipramine—rather than imipramine itself. (It has been suggested that mescaline also may achieve its effects through the action of one or more of its metabolites.)

Monomethyl nor-imipramine shows no delay in action and not only blocks the reserpine effect but in fact reverses it, causing considerable hyperactivity in test animals. At the same time, Sulser pointed out, neither imipramine nor monomethyl nor-imipramine blocks monoamine oxidase; neither increases brain levels of serotonin and norepinephrine; and neither prevents reserpine from releasing brain amines. Sulser suggested that the capacity of imipramine and its metabolites to alter cell metabolic patterns, and its antidepressant action, might depend on the ability of drugs to block free serotonin.

Other attempts to duplicate schizophrenic behaviour for experimental purposes focus on sleep deprivation. Luby of the Lafayette Clinic and Wayne State University College of Medicine, Detroit, said that the initial phases of prolonged sleeplessness—which generates such schizoid changes as depersonalization, visual hallucinations, dissociative states, and recent memory loss—were accompanied by a rise in phosphate esters in blood serum, while in later stages these decrease. He stated that this indicates changes in the high-energy phosphorylation process in which ATP plays the central role. The implication is that sleep deprivation elaborates a substance that inhibits phosphate esterification. Since similar chemical findings have been obtained in schizophrenia, the evidence tends to support the contention that biochemical processes are definitely involved in psychopathological states, especially schizophrenia.

West of the University of Oklahoma Medical Center substantiated this view by describing specific phenomena in the sequential states of prolonged (over 110 hours) sleep deprivation. Noting that sleeplessness experiments also supported the view that dreams are a necessary function more than psychodirective effort, West concluded that sleep deprivation offered a valuable model for the further exploration of mental illness.

But the precise relationship between schizophrenia and induced psychosis remains uncertain. Reasonably skilled observers can almost always distinguish one from the other. Hollister of the Veterans Administration Hospital in Palo Alto (California) stressed this point in a critical comparison of the two syndromes, noting that the hallucinations produced by psychotomimetic drugs are visual but rarely auditory. Moreover, patients know that they are unreal. Although the drugs do stimulate somatic effects, impairment of judgment and anxiety states, attitudinal changes and withdrawn behaviour are rare. The paranoid and grandiose delusions common in true schizophrenia occur infrequently. In general, the relevance of psychopharmacologic research to the etiology of true schizophrenia, while not refutable, is subject to question.

The conference also heard that women may be destined biologically to live longer than men. Men have a higher metabolic rate than women, as measured in terms of oxygen consumption, and therefore live a shorter time by the clock. Moreover, individuals can be aware of their "fast" or "slow" time. This view was expressed by Fischer of the Columbus (Ohio) Psychiatric Institute and Hospital. He stated that there is a definite relationship between life span and metabolic rate so that as metabolic rate increases, life span decreases. In effect, the mathematical product of metabolic rate and life span are a constant. The psychoactive drugs mescaline, LSD and the phenothiazines, which raise or lower metabolic rate, produce sensations in the subject of time contractions or expansions. Fischer also reported that in all animals, warm- or cold-blooded, large or small, measurement of cellular respiratory enzymes per kilogram of body mass shows total life energy, or "metabolic life", to have the same duration.

ASSOCIATION NOTES

ANNUAL MEETING NEWS

Doctors and Art

The Canadian Medical Association, in conjunction with the Montreal Museum of Fine Arts, is sponsoring an exhibition of painting and sculpture collected by some of the doctors in the Montreal area. The exhibition is being held at the Museum, 1379 Sherbrooke St. W., from June 6 to June 30. It is hoped that all doctors and their wives will visit the show. The Museum is open daily from 10 a.m. to 5 p.m. and Sundays from 2 p.m. to 5 p.m. Admission free.

L'art et les médecins

De concert avec le Musée des beaux-arts de Montréal, l'Association médicale du Canada expose au Musée, 1379 ouest rue Sherbrooke, du 6 au 30 juin, une sélection de peintures et sculptures provenant de collections personnelles d'un certain nombre de médecins de la métropole. Nous espérons que tous les médecins, ainsi que leurs épouses, se feront un point d'honneur de s'y rendre.

Le Musée est ouvert en semaine, tous les jours de 10 heures a.m. à 5 heures p.m. et le dimache de 2 heures p.m. à 5 heures p.m. L'entrée est libre.

Canad. M. A. J.
May 6, 1961, vol. 84

INFORMATION FOR CANADIAN DOCTORS ON

FINANCIAL ASSISTANCE AVAILABLE FOR GRADUATE OR POSTGRADUATE MEDICAL STUDY

in

CANADA - UNITED STATES - EUROPE

Through its Journal, The Canadian Medical Association is pleased to provide up-to-date information on financial assistance that is available to facilitate the graduate and/or postgraduate medical education of Canadian doctors. Owing to space limitations, we are not in a position to publish the complete list of medical award classifications at this time. Please refer to subsequent issues of the Journal, if the subject in which you are interested is not listed herein.

Unless otherwise indicated, the value of the awards will be quoted in the currency of the country mentioned. As entry regulations into a foreign country vary, it is recommended that the applicant for postgraduate study first investigate all details through the Embassies of the foreign countries concerned. Applicants should satisfy themselves whether medical registration in the jurisdiction of the award is or is not a requirement to hold the postgraduate post in the country selected.

In so far as entry into the United States is concerned, simply communicate with the U.S. consular office nearest your place of residence. These offices are located in the following cities: St. John's, Newfoundland; Halifax, Nova Scotia; Saint John, New Brunswick; Quebec, Quebec; Montreal, Quebec; Ottawa, Ontario; Toronto, Ontario; Windsor, Ontario; Winnipeg, Manitoba; Calgary, Alberta; Edmonton, Alberta; and Vancouver, British Columbia.

It is understood that a Canadian citizen entering the United Kingdom must have a valid passport but that no visa is necessary. Application forms for passports can be obtained at any large Canadian Post Office and should be completed and sent to the Chief Passport Officer, Ottawa, Ontario.

ANATOMY — CANADA

Name of Award	Field of Study	Where Tenable	Value	Number Available	Duration	Conditions	Apply to
Teaching Fellowships in Anatomy	Anatomy	Queen's University	$2400	Two	One year	Available annually	Professor of Anatomy, Queen's University, Kingston, Ont.
University of Toronto: James H. Richardson Research Fellowship	Anatomy	University of Toronto	$500	One	One year (renewable for not more than two years)	Graduate of an approved medical school for research in Anatomy	Professor of Anatomy, University of Toronto, Toronto 5.

ANATOMY — UNITED KINGDOM

Manchester University: Morrison Watson Fellowship	Practical and descriptive anatomy	Manchester University	Unspecified	One; next offer 1961	One year (renewable for a second)	Open to persons with a medical qualification registrable in the U.K., or a degree of an approved university	The Registrar, University of Manchester, Oxford Road, Manchester, England, prior to July 1

ANESTHESIOLOGY — CANADA

University of British Columbia: Burroughs Wellcome Fellowship	Anesthesiology: study and research in	University of British Columbia	$1000	One	Unspecified	Award made on recommendation of the Faculty of Medicine	The Dean, Faculty of Medicine, University of British Columbia, Vancouver, B.C.

BIOCHEMISTRY — UNITED KINGDOM

Liverpool University: Johnston Colonial Fellowship	Biochemistry; failing candidate in this field, pathology and physiology	Normally at the University	£400 per annum	One	One year (renewable for 2nd year)	Open to members of a Colonial university and medical school, without excluding Colonials possessing British qualifications; then open to others possessing a medical qualification or to graduates in science of approved university	The Dean, Faculty of Medicine, University of Liverpool, Liverpool 3, England, not later than June 27
London University (Lister Institute of Preventive Medicine): Grocers' Company Research Studentship	Biochemistry	Lister Institute of Preventive Medicine	*£350 p.a. 1st year; £375 and £400 in 2nd and 3rd years *Subject to revision	Unspecified. Vacancies advertised	One year (renewable for 2)	Open to British subjects	Secretary, Lister Institute of Preventive Medicine, Chelsea Bridge Rd., London, S.W.1, England
London University (Lister Institute of Preventive Medicine): Morna Macleod Scholarship	Biochemistry	Lister Institute of Preventive Medicine	*£350 p.a. 1st year; £375 and £400 in 2nd and 3rd years *Subject to revision	One. Vacancies advertised	One to three years	Open to candidates of Scottish descent	Secretary, Lister Institute of Preventive Medicine, Chelsea Bridge Rd., London, S.W.1, England

Name of Award	Field of Study	Where Tenable	Value	Number Available	Duration	Conditions	Apply to
BIOCHEMISTRY AND BIOPHYSICS — UNRESTRICTED							
The Lalor Foundation Research Grants and Awards	Biochemistry, Biophysics	North America and Western Europe	$1000 for single man or woman, $1200 for married man, working at his home institution, $1350 for married man with principal program at another institution	Twenty-one	For summer months or similar period (renewable)	The applicant should have experience and indicated research productivity corresponding to the post-doctorate level and be a member of the staff or faculty of a college or university or have equivalent position. Preferences in appointment will be given to younger members of academic staff with an upper age limit of forty-one. The work may be carried on at the applicant's own institution or elsewhere, whichever best implements the project	Lalor Foundation Inc., 4400 Lancaster Pike, Wilmington 5, Delaware, by January 16
BIOLOGICAL SCIENCES — UNITED STATES							
Yale University: (a) Alexander Brown Coxe Memorial Fellowships. (b) James Hudson Brown Memorial Fellowships	(a) Biological sciences (incl. med.) (b) Medical sciences, incl. clinical medicine and public health	Yale University	$4000 if single; $4500 if married	Unspecified	One year (renewable)	Open to university graduates who hold M.D. or Ph.D. degree; preference given to those who have previously demonstrated fitness to carry on research	Dr. Vernon W. Lippard, Dean of Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn., by January 15
CANCER — CANADA							
The Dorothy Jean Usher Memorial Scholarship for Medical Research	Preference for research studies relating to leukemia	Faculty of Medicine, University of Alberta	Income from capital endowment of $10,000	One	—	Available to graduate or undergraduate	Administrator of Student Awards, University of Alberta, before March 1
Alexander McFee Fellowship	Cancer research (rotating with physics and and chemistry)	McGill University	$1000	One	One academic year	Open to full-time candidates for higher degrees or diplomas at McGill University	Dean of Faculty of Graduate Studies and Research, McGill University, Montreal, P.Q., before May 1
H. W. Molson Fellowship	Cancer research	McGill University	$1000 per annum	One	Four years	Open to graduates of any recognized medical school. Course ordinarily comprises one or more years' study in Pathological Institute followed by clinical research	Dean of Faculty of Medicine, McGill University, Montreal, P.Q., before May 1
National Cancer Institute of Canada: Graduate Research Fellowships	Cancer research	Canada	Will depend on training and experience of candidate	Variable	One year (renewable)	Open to men and women, graduates of approved universities. Fellowships awarded to provide advanced training and experience in cancer research for individuals planning career wherein furthering knowledge of cancer will be major interest	National Cancer Institute of Canada, 790 Bay Street, Toronto 5, Ont., by December 15 of preceding year
CANCER — UNITED KINGDOM							
London University: Laura de Saliceto Studentship	Cancer	A school of the University	£150	One	Up to 5 years	Open to both sexes. The studentship is a part-time appointment and may be held in conjunction with a physiology or pathology laboratory appointment, or a clinical appointment affording special opportunities for a study of cancer	Secretary to Scholarships Committee, University of London, The Senate House, London, W.C.1, England,
Manchester University: Pilkington Fellowship	Cancer	Manchester University	£300 per annum	One, Next offer 1961	(Renewable for 2nd year or more)	Open to graduates in medicine or surgery of any approved medical school	The Registrar, Manchester University, Manchester, England, by July 1

Name of Award	Field of Study	Where Tenable	Value	Number Available	Duration	Conditions	Apply to
CANCER — UNITED KINGDOM							
James Morrison Research Fellowship	Cancer research (radiotherapy)	Sheffield National Centre for Radiotherapy	£1400 per annum	One (when vacant)	3 years	Available to nationals of all countries; must have research degree and possess high scientific qualifications and proved experience of research in radiotherapy. Award is made for the pursuit of researches into treatment of cancer by x-radiations and radioactive materials	The Registrar, University of Sheffield, Sheffield 10, England
Royal College of Surgeons: Prophit Studentships	Cancer	Royal College of Surgeons of England, or other approved institution	£1000 per annum with possible additional grant of £200 towards expenses	One	One year (renewable up to five)	Open to qualified graduates of any university	The Secretary, Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, England
Royal Society Research Fellowship	Cytology, cytochemistry with special reference to malignant cells	Unspecified	£1650 to £2050 per annum	One	Two to five years	Available to graduates; offered about every 5 years	The Assistant Secretary, Royal Society, Burlington House, London, W.1, England
CANCER — UNITED STATES							
The Jane Coffin Childs Memorial Fund for Medical Research: Fellowships: Grants	Cancer research	Unrestricted	Unspecified; determined by individual circumstances	Several	Fellowships: 1 year (renewable); Grants-in-aid: unspecified	Fellowships: Candidates must possess M.D. or Ph.D. degree or equivalent; designed to provide opportunities for training and experience in the fields bearing on cancer; Fellows expected to participate in activities of department in which they work. Grants-in-aid: Made to non-profit institutions for support of individual programs of investigation	The Jane Coffin Childs Memorial Fund for Medical Research, 333 Cedar Street, New Haven 11, Conn., by Sept. 1, Nov. 1, or March 1
CANCER — UNRESTRICTED							
Canadian Cancer Society: John S. McEachern Memorial Fellowships CATEGORY 1	Postgraduate study in diagnosis and treatment of cancer	Unrestricted subject to approval	$3600 to $4800 per annum	On basis of one per medical school in Canada	One year	Candidate shall be a graduate in medicine of approved university and shall have had not less than three years' postgraduate study of which two shall have been in a field related to the diagnosis or treatment of cancer. Must be endorsed by the Dean of Medicine. Shall accept moral obligation to practise in Canada with a particular interest in cancer	Canadian Cancer Society, 790 Bay Street, Toronto 2, Ont., by October 1
CATEGORY 2	Special training in other medical centres related to diagnosis and treatment of cancer	Unrestricted subject to approval	$15.00 per diem	Unspecified	Maximum three months	Candidate shall be a member of the teaching staff of a school of medicine in Canada	Canadian Cancer Society, 790 Bay Street, Toronto 2, Ont., by October 1
Canadian Cancer Society: Allan Blair Memorial Fellowship	To encourage junior members of clinical staff of Canadian medical schools to continue clinical investigation in the field of cancer during the early years of medical practice	In medical school of appointment	$4800 1st year; $3600 2nd year $2400 3rd year	One	Three years	Candidates should be graduates in medicine of an approved faculty and should have met the requirements for admission to the Royal College of Physicians and Surgeons of Canada. Shall have been appointed to membership without salary of the staff of one of the faculties of medicine in Canada. Shall submit a plan of work or a research project for approval	Canadian Cancer Society, 790 Bay Street, Toronto 2, Ont., by October 1

Name of Award	Field of Study	Where Tenable	Value	Number Available	Duration	Conditions	Apply to
CANCER — UNRESTRICTED							
Damon Runyon Cancer Research Postdoctoral Fellowships	Basic or applied cancer research	Unrestricted	$3600 plus $600 for each dependent. Renewals may be increased by $600 up to maximum of $6000 per year total	Unspecified; large number	One year (renewable to three)	Open to men and women holding M.D., Ph.D. or D.Sc. or who have completed all requirements leading to doctoral degree. Applicant must have demonstrated unusual ability to conduct original and independent research. Preference given to young investigators	Damon Runyon Memorial Fund for Cancer Research Inc., 730 Fifth Avenue, New York 19, N.Y., by October 1, January 1, or June 1
CARDIOLOGY — CANADA							
Joseph Schubert Memorial Scholarship	Physiology of heart, or its diseases	McGill University	$300	One	One academic year	Open to graduates of any approved medical school who are registered in the graduate faculty of McGill University and who are principally engaged in research in above field	Secretary, Faculty of Medicine, McGill University, Montreal, P.Q.
Jeannette Victor Memorial Scholarship	Physiology of heart, or its diseases	McGill University	$300	One	One academic year	Open to graduates of any approved medical school who are registered in the graduate faculty of McGill University and who are principally engaged in research in above field	Secretary, Faculty of Medicine, McGill University, Montreal, P.Q.
University of Saskatchewan: Fellowship in Cardiology	Cardiology (clinical problems)	University Hospital, University of Saskatchewan	$4000	One	One year	Candidate must have had at least two years' post-graduate training in medicine and be proceeding to specialization in internal medicine	Dr. I. M. Hilliard, Professor of Medicine, University of Saskatchewan, Saskatoon, Sask.
CARDIOLOGY — UNITED STATES							
University of Minnesota Medical School: Alpha Phi Fellowship		University of Minnesota Medical School	$2052 plus tuition and fees	One	One year (renewable)	Open to candidates who have completed one year of pediatric internship	Dean, Graduate School, 316 Johnston Hall, University of Minnesota, Minneapolis 14, Minn.
CARDIOVASCULAR DISEASE — CANADA							
McGill University: Gordon Phillips Scholarships for Research	Cardiovascular diseases	McGill University; if scholar is a graduate in Medicine from McGill, work may be undertaken at McGill or elsewhere	$1600	One	One year (renewable)	Open to graduate in medicine	Secretary, Faculty of Medicine, McGill University, Montreal, P.Q., by February 1
CARDIOVASCULAR RESEARCH — CANADA							
University of Western Ontario: The Ruth Knox Herman Fellowship (2)	Cardiovascular research	University of Western Ontario	$2000	One	Unspecified	Open to graduates in medicine from any approved Canadian university	Dean, Faculty of Medicine, University of Western Ontario, London, Ontario
University of Western Ontario: George Routledge Fellowship (2)	Research in cardiovascular diseases	University of Western Ontario	Income from endowed Fund	One	Unspecified	Open to graduates in medicine from any approved Canadian university	Dean, Faculty of Medicine, University of Western Ontario, London, Ontario
CHEST DISEASES — UNITED STATES							
American College of Chest Physicians: Resident Fellowships	Chest, heart and lung diseases	U.S.A.	Unspecified	Unspecified	One year (renewable)	Available to nationals of all countries; must have M.D. degree and adequate medical background to undertake specialized training in chest diseases. Candidates must have ECFMG certificate	American College of Chest Physicians, 112 Chestnut Street, Chicago 11, Illinois
DISEASES OF ADULT LIFE — UNITED KINGDOM							
J. C. H. Knight Fellowship	Research into social, epidemiological or preventive aspects of diseases of adult life, with special reference to problems of venereal disease, alcohol, drugs of addiction, etc.	London School of Hygiene and Tropical Medicine	£1000 a year	One	Two academic sessions	Awarded from time to time as income of trust fund permits. Applicant must be graduate of a university and either registered medical practitioners or similar qualification. Must undertake full-time research	Secretary to Scholarship Committee, University of London, Senate House, London, W.C. 1, England, not later than February 15 in year of award

Name of Award	Field of Study	Where Tenable	Value	Number Available	Duration	Conditions	Apply to
ENDOCRINOLOGY — CANADA							
American College of Physicians: Willard O. Thompson Memorial Travelling Scholarship	Endocrinology	Canada or United States	Unspecified	One	One month more or less	Candidate must be an Associate of the College; Canadians eligible. To provide an opportunity for work, young physicians to spend a month, more or less, as visiting Fellows at some institution or institutions for observation and postgraduate study	The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.
ENDOCRINOLOGY — UNITED KINGDOM							
London University (King's College Hospital Medical School): Miles-Ames Research Fellowship	Research in endocrinology	Unspecified	Not less than £750 per annum	(Not specified)	Up to 3 years	(Not specified)	The Secretary, King's College Hospital Medical School, Denmark Hill, London, S.E., England
ENDOCRINOLOGY — UNRESTRICTED							
The Endocrine Society: The Ayerst Fellowship	Study in endocrinology	Unrestricted	Total of $5000	Awarded on alternate years	Unspecified	Open to individuals possessing M.D. or Ph.D. degree or candidates for either of these degrees	Secretary, The Endocrine Society, 1200 North Walker St., Oklahoma City 3, Oklahoma, by November 1
The Endocrine Society: The Squibb Fellowship	Study in endocrinology	Unrestricted	Total of $5000	Awarded on alternate years	Unspecified	Open to individuals possessing M.D. or Ph.D. degree or candidates for either of these degrees	Secretary, The Endocrine Society, 1200 North Walker St., Oklahoma City 3, Oklahoma, by November 1
The Endocrine Society: The Upjohn Scholars	Endocrinology	Unrestricted	Not to exceed $2500 per year	Unspecified	Unspecified	Awarded to established investigators and teachers in the field of endocrinology who wish to extend their opportunities for work	Secretary, The Endocrine Society, 1200 North Walker St., Oklahoma City 3, Oklahoma
HEMATOLOGY — INDIA							
Lady Tata Memorial Trust	Research on leukemia with special reference to leukemogenic viruses in mammals, to cytological, genetical aspects, and natural history	Unrestricted	Expense grants; Fellowships £1200 per annum. Scholarships £800 per annum (full time), £400 per annum (part time)	Ten to twelve	One year (renewable)	Available to nationals of all countries. Must have medical or suitable scientific qualification and some experience of research in subject of study	Dr. D. A. G. Galton, Secretary, Scientific Advisory Committee, Lady Tata Memorial Trust, Chester Beatty Research Institute, Fulham Road, London, S.W.3, England
INFECTION AND IMMUNITY — UNITED STATES							
James W. McLaughlin Predoctoral Fellowship	Infection and immunity	The University of Texas Medical Branch, Galveston, Texas	$3600 plus dependency allowances	Availability depends upon availability of funds	One year (renewable for a maximum of 2 years)	Exceptionally well-qualified individuals who meet the requirements for admission to the Graduate School of the University of Texas	Chairman, McLaughlin Committee, The University of Texas Medical Branch, Galveston, Texas
James W. McLaughlin Postdoctoral Fellowship	Infection and immunity	The University of Texas Medical Branch, Galveston, Texas	Stipend in line with academic level of Fellow	Availability depends upon availability of funds	One year (renewable for a maximum of 2 years)	Applicant must hold doctoral degree and have appropriate training and experience, related to field in which research is to be done	Chairman, McLaughlin Committee, The University of Texas Medical Branch, Galveston, Texas

(To be continued)

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

It appears that a certain amount of dissatisfaction has been expressed by members of the Association who attended the Toronto meeting of last year, to the effect that having paid their membership fee of five dollars in June, 1910, they were asked in January, 1911, to pay a further five dollars. They had assumed that the five dollar fee included the subscription price of the Journal of the Association, which was about to be published, and when it did not appear until January, 1911, they further assumed that they should receive the Journal until June, 1911. To those who have expressed this sense of dissatisfaction, and to others who perhaps have felt it without expressing it, the finance committee desires to offer a word of explanation and to add a word of apology.

The fee of five dollars paid in June, 1910, was the membership fee of the Association for the calendar year January to December, 1910. This fee carried with it the right to receive the Journal of the Association when it should appear. It was hoped that it would appear shortly. That it did not until January, 1911, was unfortunate, but unavoidable.—*Canadian Medical Association Journal*, 1: 460, May 1911.

CONNAUGHT

HEPARIN SODIUM INJECTION

For *Immediate* Treatment

of impending

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10,000 Units (approx. 100 mg.)

INTRAVENOUSLY

Supplied in packages of 5 x 1-cc. ampoules—each cc. contains 10,000 International Units.

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5 x 10-cc. vials— 1,000 International Units per cc. (approx. 10 mg./cc.)
5-cc. vial —10,000 International Units per cc. (approx. 100 mg./cc.)

Reference:

Intravenous Heparin—Its role in the Management of Acute Thromboembolic Diseases.

W. Ford Connell and George A. Mayer
Applied Therapeutics, May 1960, Vol. 2, No. 5, 371-375.

CONNAUGHT MEDICAL RESEARCH LABORATORIES
UNIVERSITY OF TORONTO
TORONTO 4, CANADA

Established in 1914 for Public Service through Medical Research and the development of Products for Prevention or Treatment of Disease.

Canad. M. A. J.
May 6, 1961, vol. 84

BOOK REVIEWS

1960-1961 YEAR BOOK OF MEDICINE. Edited by Beeson Muschenheim and others. 708 pp. Illust. Year Book Publishers, Inc., Chicago, 1960. $8.00.

This current volume maintains the usual high standard of this series. The articles abstracted give a good cross-section of clinical investigative interest in internal medicine that are required reading for the well-informed internist. There is much of value to the general practitioner. Browsing by other specialists should prove rewarding.

While the selection of articles reflects the special interests of each sectional editor, this proves no disadvantage because of their breadth of interest. Many of the abstracts are rendered of greater value by the editorial comments.

Altogether this is a meaty and stimulating volume, particularly as a source book for the more detailed study of articles referred to, which would be necessary in every instance before the information were applied in one's practice.

TOBACCO: EXPERIMENTAL AND CLINICAL STUDIES. P. S. Larson, H. B. Haag and H. Silvette. 932 pp. The Williams & Wilkins Company, Baltimore, Md., 1961. $20.00.

There is no question that the use of tobacco has become one of the more controversial features of medicine in the twentieth century. In particular the material presented in Chapter 21 of this book, dealing with neoplastic disease, is currently most controversial. The authors state, "The question of whether tobacco-smoking or other tobacco use produces cancer has not unnaturally exercised the pens and imaginations of medical writers for almost a century," and further, "Publications on this subject have now grown so numerous, however, that the most recent writers usually content themselves with reviewing again and again the increasingly cumulative summaries of the relationship of tobacco to cancer of one particular site."

It is suggested by the authors that from a scientific point of view the most important information that statistical studies cannot provide is proof of causality; and from the practical point of view such studies cannot furnish or predict the carcinomatous fate of the individual patient, smoker or non-smoker. It is this last consideration, of course, which permits John Doe to smoke safely, to drive automobiles safely, to go off to war and return safely, regardless of the calculated or statistical chance. In other words, the answer to statistics, according to the authors, is: "It can't happen to me!"

With the possible exception of the chapter dealing with neoplastic disease, the book is presented in a most objective manner. It certainly represents the most exhaustive monograph on tobacco that could be created.

The organization in the book is excellent. It makes possible quick and easy reference. It should prove useful to teachers of pharmacology, to research workers who are interested in any field related to tobacco, and to clinicians.

A compilation of this sort is an extremely tedious and time-consuming effort and the authors deserve considerable credit for their perseverance. Also they deserve credit for the form of writing, which is very good, and for the care that has gone into the checking for accuracy.

However, as the authors state, they were "deliberately non-selective, printing (as it were) good work and bad, sound and uninformed opinion, alike, in the same size type". Such a presentation draws together a tremendous volume of work but does not in itself present anything new or even make it possible for the reader to draw conclusions.

Had the authors set forth to screen the material and write a book on tobacco—rather than a monograph—it would seem that a much more useful compilation would have resulted.

As a book on tobacco this book would certainly appear to be complete and the authors are to be commended for their thoroughness. The text should find considerable use as a source of reference material.

FUNDAMENTALS OF NERVE BLOCKING. Vincent J. Collins. 354 pp. Illust. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1960. $9.50.

The first 200 pages of this book provide a background of the principles and problems of nerve blocking which are understood and appreciated by the author, whose large pain clinic at Bellevue Hospital, New York, is well known. The chapters describing disease states for which blocks may be considered, and the anticipated degree of success following the use of such procedures, are written with the authority provided by experience.

The remainder of the 354 pages contains detailed descriptions of block techniques of interest and practical value. Useful illustrations have been reproduced from well-known sources.

If the enumerated paragraph headings found under each chapter title throughout the volume had been repeated for the individual chapters in the table of contents, this would have been of much greater value in a book which will be primarily for reference.

An anesthetist with space in his library for a volume on nerve blocking would do well to have a look at this moderately sized book.

SOURCE BOOK OF MEDICAL HISTORY. Edited by Logan Clendening. 685 pp. Dover Publications, Inc., New York; McClelland & Stewart, Toronto, 1960. $2.75.

This is a republication of Dr. Clendening's book of 1942, which puts together chronologically 124 papers by 120 authors describing their individual contributions to medicine, ranging in time from the Egyptian papyri to Roentgen's paper "On a New Kind of Ray", published in 1895.

Dr. Clendening precedes each chapter with a brief summary of the history of the subject to be illustrated, and a list of references to publications from which the reader may obtain detailed information. Extracts from the works of laymen, such as Chaucer, Molière, Dickens and Thackeray, give these authors' observations of the medical profession of their times.

There is an excellent index.

(Continued on page 1049)

(Continued from page 1044)

CLINICAL APPLICATIONS OF CARDIOPULMONARY PHYSIOLOGY. M. Henry Williams, Jr. 233 pp. Illust. Paul B. Hoeber, Inc., New York, 1960. $7.50.

Pulmonary and cardiac functions are usually considered to be distinct and separate entities, and textbooks of physiology, pathology and medicine present diseases of the heart and lungs as separate pathophysiological processes. Moreover, the clinical approach to the study of these organs has resulted in the evolution of "cardiologists" and "chest physicians" as further emphasis upon the distinction between the two systems. Many physiologists and some clinicians regard this dichotomy as artificial and undesirable; Dr. Williams, the author of this book, is one of these.

In emphasizing the unity of cardiopulmonary physiology, Dr. Williams presents a more logical approach to the study of this subject in the diagnosis and treatment of diseases of the heart and lungs. The book provides clear and concise descriptions of the various techniques and procedures available. It outlines the physiological bases for the abnormal findings characteristic of the various cardiac, pulmonary and cardiopulmonary diseases. At all times, the author gives paramount importance to the intimate relationship between the heart and lungs, and he shows how abnormal laboratory results in pulmonary or cardiac function may influence other apparently unrelated findings.

This book is intended to be a useful clinical guide for physicians. As such, it is to be highly recommended. The author avoids controversial theoretical questions in this field and he has succeeded in presenting the material without becoming involved in the mathematics which seems to be so common in much of the literature on this subject.

On the other hand, the book will not appeal to the few who are engaged in basic or clinical research in this subject. Of necessity, only the fundamental and well-established concepts are outlined. Many of the "normal" values listed are averages only. The diffusing capacity is presented as a membrane function only. The explanation of the mechanism of dyspnea, as outlined, is questionable (certainly it is controversial). Many will not agree with the author's views on the pathogenesis of pulmonary hypertension. The physiological adaptations which occur during muscular exercise are well outlined, but their interrelationship and the possible mechanisms of cause and effect are not discussed.

To state these "unfavourable" features should not detract from the value of this book. The author did not intend it to be a detailed discussion of all aspects of cardiopulmonary physiology. It is an excellent synthesis of basic cardiopulmonary physiology, concise, comprehensible and accurate. The medical profession will welcome this work which treats the study of cardiac and pulmonary functions as a unified science. The appearance of this book is particularly appropriate at this time, when more exact evaluation of patients suffering from deranged cardiopulmonary function is so important. Many conditions, such as congenital heart disease, are correctible in selected patients. Physicians will find Dr. Williams' book an invaluable guide in their evaluation of such individuals.

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MEDICAL NEWS *in Brief*

(Continued from page 1030)

TWELFTH INTERNATIONAL HOSPITAL CONGRESS

The Twelfth International Hospital Congress, organized by the International Hospital Federation, with the assistance of an Italian Organizing Committee, will take place in Venice from June 5 to 9, 1961, under the chairmanship of Avv. Luigi Colombo, honorary president of the F.I.A.R.O. (Italian Hospital Federation). The Congress headquarters will be in the Cultural Centre of the Giorgio Cini Foundation on the Island of S Giorgio Maggiore, Venice, where all the Congress sessions and business meetings will be held, apart from the opening ceremony which will take place in the "Sala dello Scrutinio" at the Doge's Palace in Venice. A lounge will be provided on the Island for participants and their guests, and refreshments will be available. The Island is served by a regular steamer service and, in addition, special arrangements will be made at peak periods.

The central theme of the Congress will be "The changing role of the hospital in a changing world". This broad theme will be subdivided to deal with three specific problems of particular interest. These will be (1) Changing methods of financing hospital care, which will include the four main types – private resources, taxation, compulsory and voluntary insurance, how these have arisen from the social systems in the various countries, their advantages, disadvantages and problems; (2) Changing characteristics of patient care, with particular reference to outpatient services, comprehensive patient care, early ambulation within the hospital and regionalization of hospital services; and (3) Changing characteristics of hospital planning and construction, as regards control and supervision of hospital plans, the use of standard elements in hospital construction, planning in accordance with new concepts in the management of supplies and stores, and the effect of advances in patient care on hospital design.

Meetings of the General Assembly of Members, the Council of Management, the Executive Committee and the officers of the International Hospital Federation will be held during the Congress, to deal with the business of the Federation.

The following exhibitions are be-

(Continued on page 32)

FOR OFFICE AND INSTITUTIONAL USE
along the continuum from mild anxiety to severe psychosis.

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DOSAGE GUIDE	USUAL	RANGE
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non-hospitalized psychotics	25 mg. t.i.d.	(75-200 mg.)
hospitalized psychotics	100 mg. t.i.d.	(200-800 mg.)
behaviour problems in children	10 mg. b.i.d.	(20-40 mg.)

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Lifts depression...as it calms anxiety!

Smooth, balanced action lifts depression as it calms anxiety...rapidly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

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Acts swiftly – the patient often feels better, sleeps better, within a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

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Diet methods usually decrease cholesterol levels only slightly. To successfully lower cholesterol levels, its production by the body must be inhibited. MER/29 is the first agent proved to safely limit cholesterol biosynthesis.

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In some patients, fewer and less severe anginal attacks; improved ECG patterns; diminished nitroglycerine requirements; improved sense of well being.[4-8]

Long-term studies are an absolute necessity to determine the over-all prognostic significance of any observation that mortality rates may be reduced following coronary thrombosis. Thus far, one study[2] of a year's duration, has offered a report of this type.

...safety data: Because of long-term therapy, periodic examination of patients may be desirable.

...contraindicated: During pregnancy, because cholesterol plays an important role in the development of the foetus.

...dose: One 250 mg. capsule daily, before breakfast. Available in bottles of 30.

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TRADEMARK: MER/29

MEDICAL NEWS *in brief*
(Continued from page 27)

ing organized by the Italian Organizing Committee:

(1) A hospital equipment and medical care exhibition, to be held in the large gymnasium next to the plenary session hall and in the gardens of the Island of S. Giorgio Maggiore.

(2) An Italian hospital architecture exhibition, comprising plans, photographs and models of new hospital buildings recently completed or under construction.

(3) An exhibition on the history of the old hospitals of the Venetian Republic; exhibits will include art treasures belonging to the most important hospitals of Italy. It will be held in the historic 15th century rooms of the "Scuola Grande di S. Marco," at the entrance to the Civic Hospital of Venice.

All those interested in any branch of hospital and health service, whether members of the International Hospital Federation or not, may participate in the Congress. Members of participants' families registered as Congress guests will be invited to take part in social functions. They may also attend the opening ceremony at the Doge's Palace, but it will unfortunately be impossible to admit them to any other Congress meetings. They will be able to take part in organized sightseeing tours and excursions during the Congress meetings.

All enquiries regarding the Congress, *except* those relating to travel or accommodation, should be addressed to: International Hospital Federation, 24/26 London Bridge Street, London, S.E.1, England.

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RESEARCH IN MEDICAL CARE AND HOSPITAL ADMINISTRATION, UNIVERSITY OF PITTSBURGH

The University of Pittsburgh recently received a seven-year grant from the U.S. Public Health Service for a research program in medical care and hospital administration. The award, totalling $734,144, has been made to the University's Graduate School of Public Health to support research activities in the general areas of: (1) manpower for medical and hospital services, (2) the utilization of medical and hospital services, and (3) the development and evaluation of medical care programs.

Dr. Cecil G. Sheps, professor of medical and hospital administration and director of the Program in Medical and Hospital Administration, is the principal investigator. Dr. Sheps is a graduate of the University of Manitoba Medical College and former Clinical Professor of Preventive Medicine at Harvard Medical School.

Of the many individual projects being considered, Dr. Sheps listed these five specific areas to be included in the program that will be conducted under this grant: (1) hospital utilization as affected by the doctor, patient and hospital; (2) the changing role of the hospital emergency unit; (3) an analysis of the scope of service for hospitals of differing size and location; (4) the changing patterns of patient care in response to new knowledge, such as the role of new medical and allied specialties and auxiliary personnel; (5) problems of optimal utilization of health personnel.

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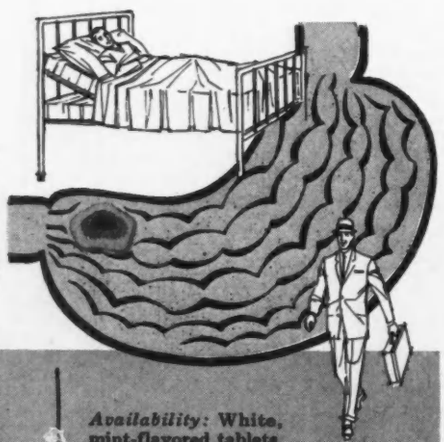

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